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2 IN THE UNITED STATES DISTRICT COURT
3 IN AND FOR THE DISTRICT OF DELAWARE
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5 VANDA PHARMACEUTICALS, INC,) CIVIL ACTION
Plaintiff,)
6 v.) NO. 18-651-CFC
7)
TEVA PHARMACEUTICALS USA,)
8 INC., et al.,)
9 Defendant.)

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14 Wilmington, Delaware
15 Wednesday, March 30, 2022
16 Bench Trial Transcript
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18 BEFORE: HONORABLE COLM F. CONNOLLY, Chief Judge
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24 Michele L. Rolfe, RPR, CRR
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P R O C E E D I N G S

(REPORTER'S NOTE: The following bench trial was held in Courtroom 4B, beginning at 8:30 a.m.)

THE COURT: Good morning. We have some housekeeping matters apparently.

MR. ROZENDAAL: Yes. Good morning, Your Honor.

Two matters that I'm aware of. The first is the issue of the closings. We have talked about the scheduling of that and I think the parties are in agreement that it would be beneficial for everyone to schedule those after the post trial briefing has been completed.

THE COURT: I mean, we're going to see. I might have questions for you, so you should be ready. So the answer is we'll wait and see. And I may just decide, as I often do, that I'd like to hear some issues right away, so okay.

MR. ROZENDAAL: Understood. I guess the thinking that we had talked about yesterday is that there are some legal issues that are sort of percolating up through the case now that we're seeing how the evidence is coming in and that it might be easier to deal with those after the -- they have been --

THE COURT: It may be, and it may be that you submit the briefing and I just decide I don't need to have

1 oral argument or I might need to. We'll see.

2 When's the launch? Is that public?

3 MR. ROZENDAAL: I think everyone agrees that the
4 compound patent lasts at least until December.

5 THE COURT: Okay. So I have some time in this
6 case.

7 MR. GROOMBRIDGE: Your Honor, the Court has
8 until December. I don't remember the exact date within
9 December, but it's in the month of December.

10 THE COURT: All right.

11 MR. ROZENDAAL: And then the one other thing is
12 an evidentiary -- an exhibit objection that we wanted to
13 make. So there is a -- Vanda has put on its list for use
14 with Dr. Bergmeier, their chemist, a prior art reference
15 that is the Singh, S-I-N-G-H. It's DTX-52.

16 And that was a reference that had been relied
17 upon by defendants in part of an obviousness combination to
18 a different patent that is no longer in the case. And so we
19 object to the use of it here on relevance grounds because we
20 don't know --

21 THE COURT: All right. So wait. So your expert
22 is going to testify, apparently offer an opinion about
23 another patent that's no longer in the case? No?

24 MR. ROZENDAAL: No, I think their expert is
25 going to testify about a prior art reference that we had

1 used against a patent that is no longer in the case and we
2 don't think that's relevant to anything that is still in the
3 case.

4 THE COURT: All right.

5 MR. ROZENDAAL: That's the issue.

6 MR. GROOMBRIDGE: And, Your Honor, the -- this
7 goes to Dr. Bergmeier and the question is simply -- Your
8 Honor may remember yesterday there was some -- Dr. Perni,
9 the defendant's expert, had at least some doubt about --
10 perhaps, about when Bristol-Myers Squibb had disclosed
11 publically the process. I had asked him about that and he
12 said it was publically available and then on redirect he
13 said maybe he wasn't sure about the date.

14 And the sole purpose for this is to show that
15 BMS had made that -- a public disclosure before the priority
16 date and that that -- he's not going to talk about anything
17 else, but that was in his expert reports on the earlier
18 patents, right, to say this is a reference that discloses
19 the follow and this is the date.

20 And that's all --

21 THE COURT: So it does seem -- I was a little
22 confused, frankly. You're trying to bring out that BMS
23 disclosed it earlier than they did?

24 MR. GROOMBRIDGE: Correct.

25 THE COURT: Which normally it would be the

1 opposite, right, so I did have to say when it was coming in
2 yesterday, I'm thinking to myself, well, I'm missing
3 something big here, but I'll figure it out later on.

4 MR. GROOMBRIDGE: Maybe it's useful if I give
5 it --

6 THE COURT: Go ahead --

7 MR. GROOMBRIDGE: The issue here is -- as I
8 understand their argument, it's along these lines is that
9 this aspect of the process --

10 THE COURT: What aspect?

11 MR. GROOMBRIDGE: The part where you take the
12 carboxamide and you react it with something to get the
13 methenamine, which is what we've all been focused on in the
14 process steps.

15 THE COURT: Right.

16 MR. GROOMBRIDGE: They're saying, I believe,
17 that you, Vanda, got that from BMS. You didn't come up with
18 that yourself.

19 THE COURT: Okay.

20 MR. GROOMBRIDGE: Right. And that's, in their
21 view, I think the reason why they're saying so someone from
22 BMS should be an inventor on this patent.

23 What we're saying is the priority date of this
24 patent is 2014. That aspect of the process was out in the
25 public domain long before this. And just because a prior

1 art has then published and someone else later came along and
2 builds something, that does not make the prior artist then
3 an inventor. You know, that's the law, right.

4 You don't get to say because I made -- I created
5 this and made it public, if you later on use it and get a
6 patent, I'm an inventor on your patent.

7 THE COURT: What did you just say?

8 MR. GROOMBRIDGE: I'm obviously going too fast.

9 THE COURT: It was just the last sentence. You
10 said "obviously something" and then I lost you.

11 MR. GROOMBRIDGE: So in our view, if that aspect
12 of the process was something that was known in public before
13 the priority date of this patent, then it would not make BMS
14 or any other prior -- person who had published the process
15 an inventor; it would simply mean that the Vanda people have
16 taken that information and built on it.

17 THE COURT: Okay.

18 MR. GROOMBRIDGE: And that's why, for example,
19 there's a debate whether the normal roles are reversed.

20 THE COURT: Right. Okay.

21 MR. GROOMBRIDGE: The patent holder is saying --

22 THE COURT: Right. I get it. In other words,
23 your point is they're just building what's out there in the
24 art. You're not claiming that's inventive. That's part of
25 the process.

1 MR. GROOMBRIDGE: Right, okay.

2 THE COURT: Before you go, what did Ms. Platt
3 contribute to the invention?

4 MR. GROOMBRIDGE: I believe, and it's -- I'm not
5 the expert or the -- on this --

6 THE COURT: No, but you're lead counsel. You
7 heard it. What did she --

8 MR. GROOMBRIDGE: I think what she contributed
9 is intellectual input -- basically, the way Vanda works is
10 it's working with these contract manufacturers and the
11 contract manufacturers are doing the work. And the
12 scientists at Vanda are saying -- analyzing what they get
13 back and saying do this, do that.

14 THE COURT: What did she do? Other than just do
15 mathematics, what did she do?

16 MR. GROOMBRIDGE: I think she provided guidance
17 about how they would identify these impurities.

18 THE COURT: What kind of guidance -- I listened
19 to her deposition, like what did she do?

20 MR. GROOMBRIDGE: I do not know the answer, Your
21 Honor.

22 THE COURT: Yeah, well, neither do I. All
23 right. Let's hear from the other side.

24 MR. ROZENDAAL: Your Honor, so I think our point
25 is, now that we know what they are planning to use it for,

1 our point is that in their expert's report on the topic of
2 inventorship, they never said inventorship is not a problem
3 because we didn't get this from BMS because it was somehow
4 already out in the public. That would be an undisclosed
5 expert opinion that we would be hearing here for the first
6 time.

7 So --

8 THE COURT: Okay. So that's a Rule 26 argument.
9 In other words, it's -- he didn't disclose this opinion
10 before?

11 MR. ROZENDAAL: He didn't disclose this opinion
12 before.

13 THE COURT: All right. So let's hear then.
14 Did you disclose it before?

15 MR. GROOMBRIDGE: I think we disclose -- he's
16 not going to testify, Your Honor, about inventorship. He's
17 simply going to say this is a piece of prior art that
18 discloses the following and it was publically available.
19 Now, this may all be a tempest in a teacup because, frankly,
20 the only reason we're doing this, it seemed like there was
21 some debate yesterday. But I'd like to go back and look at
22 his expert report and see whether we think we even need it.

23 THE COURT: I mean, here's -- how's -- what's
24 the proffer? All he's doing is -- basically, you're having
25 him be the vehicle by which you introduce this article.

1 MR. GROOMBRIDGE: Yes, about which he -- opined
2 in his expert reports.

3 MR. ROZENDAAL: On a different patent that's no
4 longer in the case, never in connection with the --

5 THE COURT: I get the opinion, right, but really
6 isn't -- isn't what we're really talking about a fact issue?
7 It's that they'll be -- if there's a prior art out there
8 that BMS [sic] disclosed this process in, unless I have to
9 do, you know, mental gymnastics to figure it out myself or I
10 need expert help, it's just a fact question whether it was
11 disclosed or not.

12 And in which case, why do you even need -- for
13 instance, if they wanted to in rebuttal, presumably, they
14 can have a fact witness come in and say, here's the article,
15 right. And they can get the article into evidence. Or
16 maybe they can do it on cross-examination of your witness.
17 And it's just getting the article into evidence.

18 Or is it more than that? Is it that, no, the
19 article would require an expert to interpret it to explain
20 to me that this is BMS's procedure being disclosed, which
21 probably is the case, but --

22 MR. ROZENDAAL: I was about to say, I don't want
23 to presume what Your Honor would or wouldn't glean but from
24 the article, without some expert elucidation it would be
25 difficult to establish what the article really teaches. So

1 I think that's why they're trying to sneak it in with the
2 expert and he's never talked about that in connection with
3 the --

4 And I would say, look, the whole reason we're
5 doing the inventorship is we know that BMS's process
6 produced a 99.9 pure batch of tasimelteon. So BMS had a
7 process that satisfied all the purity requirements but it
8 was confidential. It wasn't public prior art. And that's
9 why we're not talking about anticipation on that batch.

10 And so our point is, they did it. You got it
11 from them and then you tried to get a patent on it later.
12 And they never said, oh, no, we didn't get it from them. It
13 was in the prior art. So the fact that we're being
14 confronted with this for the first time seems a little odd
15 to us, but...

16 THE COURT: All right. Hold on. First of all,
17 to be clear, we're talking about which patent?

18 MR. ROZENDAAL: '465, Your Honor.

19 THE COURT: And your point is that BMS's
20 tasimelteon --

21 MR. ROZENDAAL: They're --

22 THE COURT: -- reads on Claim 1, if you accept
23 their interpretation of the reduction claim, assuming that
24 you can have two-step -- sorry -- yeah, assuming that
25 contacting and reacting is a -- is read the way the

1 plaintiffs want to read it, which is that you can actually
2 have two steps as opposed to one step, right?

3 MR. ROZENDAAL: Correct.

4 THE COURT: Your point would be BMS's
5 tasimelteon reads on Claim 1.

6 MR. ROZENDAAL: Yes.

7 THE COURT: Okay. All right. And the only
8 reason it's not anticipation because it -- a piece of prior
9 art wasn't out there to be had. But because of their
10 relationship, "their" being plaintiff's relationship with
11 BMS, they had full access to this and they knew it and
12 they've done nothing new.

13 MR. ROZENDAAL: Correct.

14 THE COURT: Right. Okay.

15 MR. ROZENDAAL: And if they had told us earlier,
16 no, we didn't get it from BMS, we got it from some
17 publication, then we would have presumably a different set
18 of expert reports and a different set of evidence in front
19 of the Court.

20 THE COURT: All right. And your theory is,
21 Mr. Groombridge, that BMS had made tasimelteon, but the
22 identifications of these purity specifications was done
23 solely by Vanda people and, therefore, they should be
24 credited with inventorship.

25 MR. GROOMBRIDGE: Yes, Your Honor, what we think

1 that Vanda brought to the party is the work which, as we
2 heard, took several years to actually figure out the
3 identity and structures of these materials. And I think
4 there may be a difference of opinion -- with BMS, as I think
5 the evidence has established, never did.

6 And so I think there's also a dispute between
7 the parties about what would actually be necessary in order
8 to be -- to have invented this. Does it involve knowing the
9 structures of the things or does it not, right?

10 But one way or another, in our view, the
11 process, or at least the aspect of the process that BMS was
12 using, that is recited in the claim, was out in the public.
13 And Vanda -- that doesn't make BMS an inventor.

14 THE COURT: Did BMS invent tasimelteon?

15 MR. GROOMBRIDGE: Yes.

16 THE COURT: What in Claim 1 did BMS not invent?

17 MR. GROOMBRIDGE: The identification of the
18 impurities.

19 THE COURT: Anything else?

20 MR. GROOMBRIDGE: There's nothing that I'm
21 thinking of right now, Your Honor.

22 THE COURT: I mean, I know we have had a lot of
23 testimony and I'm going to show how ignorant I am in a sense
24 that I can only digest so much when I listen to all of this.

25 But going back 30,000 feet, how is it inventive

1 to identify an impurity in a chemical?

2 MR. GROOMBRIDGE: So, as I think we saw
3 yesterday, Your Honor, the guidelines, for example,
4 recognize that there may be impurities for which it's simply
5 not feasible to identify them because it's a challenge. And
6 that is what the Vanda people were working on, was -- and
7 BMS had worked for years and have been unable to do this.
8 And the -- or they had tried, but in our view, they either
9 couldn't do it or got it wrong.

10 And what -- knowing the structure of the
11 impurities has great value because what it does is it makes
12 it much easier to control your process. Also makes it
13 easier to know that these things are not going to poison
14 someone. You can look at it, you can test it, for example,
15 synthesize it, run it through the process, see if it has
16 negative effects.

17 And in our view, that's why FDA was saying to
18 both Teva and Apotex, you need to -- these impurities are
19 reported in the literature. You need to manage your process
20 to make sure that you're controlling for them and that was
21 only possible because Vanda had identified them.

22 And so, there is, in this field of making a
23 commercial-grade pharmaceutical, tremendous value to knowing
24 what it is that could be produced as potentially toxic
25 byproduct. And that's what Vanda was doing and that's

1 what -- certainly, Ms. Platt was involved in that. And
2 that's what the other two inventors were also working on and
3 it was --

4 THE COURT: But if the overall aggregate
5 impurities is so small that the FDA has already said it's
6 not going to affect anyone's health, how does it contribute
7 to anything in any way?

8 MR. GROOMBRIDGE: Well, the only reason the FDA
9 could say that about these impurities was because Vanda had
10 identified them and shown to FDA that they would not do
11 that. In other words, when the FDA said that, it had the
12 benefit of the work that Vanda had done that's embodied in
13 this patent.

14 THE COURT: Was there tasimelteon on the market
15 before this patent issued?

16 MR. GROOMBRIDGE: No, and the entire -- well,
17 before the patent issued it may have been, but it wasn't on
18 the market before --

19 THE COURT: I thought it was on the market
20 before.

21 MR. GROOMBRIDGE: The patent was -- I mean, the
22 patent was filed in 2014, and I don't remember -- I believe
23 tasimelteon was launched that year, right.

24 But the work that underlies the patent was done
25 by Vanda as part of the claim to get the process of

1 tasimelteon to the point it could be FDA approved. In other
2 words, the work that's described in the patent is a direct
3 result, came from what the folks at Vanda did in order to
4 get this to a point where it was FDA approvable; and that's
5 why the patent even exists.

6 THE COURT: If I conclude at the end of this
7 trial that Ms. Platt is not an inventor, do I even need to
8 get into any of this?

9 MR. GROOMBRIDGE: Well, Your Honor, they have
10 not argued invalidity based on that Ms. Platt is not an
11 inventor.

12 THE COURT: Well, they've argued invalidity
13 based on lack of inventorship.

14 MR. GROOMBRIDGE: And, in fact, this was an
15 issue that we covered in the meet and confer.

16 THE COURT: Who's the "we?" Not me, right?

17 MR. GROOMBRIDGE: No, no, that counsel covered.

18 That what they've argued, and we specifically
19 asked, are you saying that the patent is invalid because the
20 Vanda inventor should not be on it, or are you saying that
21 it's invalid because they should be on it but also someone
22 from BMS should be on it, and the answer is, there's a
23 missing coinventor.

24 Now, another issue that always comes up when we
25 talk about these things, Your Honor, is that inventorship is

1 correctable; so that if it turns out that Ms. Platt was not
2 an inventor of this, Vanda could simply go to the patent
3 office and say, please revise the patent and take her off.

4 You know, the whole purpose of the inventorship
5 rules is to prevent -- is to not have patents be held
6 invalid because there's been a mistake in putting someone
7 on, you know. And so, if Your Honor were to conclude that
8 she's not an inventor, it would be correctable.

9 But, frankly, had they made the argument that
10 it's not -- it's invalid because she shouldn't be an
11 inventor, we would have presented a very different case. We
12 would have called her here and said, what did you do, right?
13 Like, what did you do? Right? That was never put in issue.
14 And, frankly, we thought, you know, it doesn't matter. No
15 one is arguing there's a problem, right?

16 What they did was take a series of snippets of
17 her deposition that seemed to create the impression that she
18 did nothing.

19 THE COURT: And it did that, that's for sure.

20 MR. GROOMBRIDGE: And if they had -- but even if
21 that were true, right, that's a correctable problem. Had
22 they said to us, we think you've got a problem with your
23 patent because she's not an inventor, one of the things we
24 could have done would have been to go to the patent office
25 and simply say, just take her off, right.

1 THE COURT: But then under that theory, you
2 could just go back and give credit to BMS.

3 MR. GROOMBRIDGE: I think that's probably right,
4 Your Honor, because remember BMS has effectively licensed
5 all the rights in tasimelteon to Vanda. So that even if
6 some individual at BMS were an inventor, right, then BMS
7 would be contractually obligated to help us fix the problem.

8 And so the -- in our view, I mean, this is part
9 of what's wrong with the inventorship argument, is at the
10 end of the day, right, it doesn't change anything because
11 this product was essentially sold by BMS to Vanda with all
12 of the rights around it. And if BMS has some of those, then
13 they came to Vanda in that contract.

14 MR. ROZENDAAL: Your Honor, may I respond?

15 THE COURT: Sure.

16 MR. ROZENDAAL: So, first of all, I think the
17 record will show that tasimelteon was FDA approved before
18 the priority date of the '465 patent. So the suggestion
19 that the '465 patent somehow contributed to the ultimate FDA
20 approval I don't think is borne out by the chronology of
21 events.

22 Second of all, the hypothesis that BMS was
23 somehow trying to identify these impurities and worked on it
24 and couldn't do it, I don't think there's any evidence in
25 the record to support that. I think the evidence in the

1 record is that BMS succeeded in making extraordinarily pure
2 tasimelteon and that nobody at BMS or the FDA or anywhere
3 else cared what the tiny fractions of impurities were in it.

4 Then when Vanda got the product, I think the
5 testimony was pretty clear that Vanda said to two contract
6 manufacturers, Shasun and Formosa, hey, make this stuff.
7 And in the course of making it, they produced HPLC
8 chromatograms that showed impurities, and Ms. Platt
9 essentially said to them, hey, Formosa, what's in this peak
10 in the chromatogram? And then it was characterized.

11 I think that was the extent of her contribution.

12 Mr. Groombridge is correct that the focus of our
13 improper inventorship argument is on the omission of the BMS
14 inventors and although it is theoretically possible that
15 that is something that could be corrected, if they could
16 find the right inventors and agree to put them on the patent
17 some day, unless and until they do that the patent is
18 invalid.

19 Now, this is all, of course, on top of the fact
20 that we think the patent is invalid is obvious anyway,
21 right, because we don't think the -- rummaging, as I said in
22 the opening, rummaging in the dustbin of history and sort of
23 seeing what impurities had already been removed from the
24 process we don't think is something that patentable because
25 the idea of coming up with highly pure tasimelteon is an

1 obvious thing to do.

2 But that's the outline of the argument.

3 THE COURT: All right. So then let's go back,
4 then, to the issue that gave rise to all of this. But this
5 is very helpful.

6 So we had, you know, equivocal or ambiguous
7 testimony yesterday about, well, when did, actually, BMS
8 publically disclose this, right? That's a fair
9 characterization, right?

10 MR. GROOMBRIDGE: I think so, Your Honor, yes.

11 MR. ROZENDAAL: I would agree with that, Your
12 Honor.

13 THE COURT: So the question is, do we want to
14 get clarity on that point? And so -- I forgot already.
15 Mr. Groombridge, you're proposing to, on cross-examination
16 of their expert, bring this --

17 MR. GROOMBRIDGE: No, on direct.

18 THE COURT: You're bringing your expert in
19 rebuttal.

20 MR. GROOMBRIDGE: Yes.

21 THE COURT: And she or he?

22 MR. GROOMBRIDGE: He.

23 THE COURT: He is then going to be asked to
24 identify an article that, according to him, disclosed the
25 process by which BMS made this molecule --

1 MR. GROOMBRIDGE: Yes, the --

2 THE COURT: -- or compound, whatever you want to
3 call it?

4 MR. GROOMBRIDGE: Yes, that's correct. And
5 simply say, this is from BMS and it discloses this -- a
6 process with tasimelteon that includes a reduction of
7 carboxamide methenamine.

8 And, frankly, Your Honor, this wasn't -- we were
9 surprised it was even a dispute; we learned about it this
10 morning, and --

11 THE COURT: Wait. There was a dispute that you
12 could do this, you mean?

13 MR. GROOMBRIDGE: Yeah, that there was an
14 objection to this.

15 MR. ROZENDAAL: Well, the exhibit was disclosed
16 a day late, so...

17 THE COURT: Right.

18 MR. STONE: Your Honor, if I may, the witness
19 for BMS who testified about this, Dr. Perni, testified on
20 his redirect examination that he didn't know when it was
21 disclosed. At his deposition he had admitted that this
22 reference is, in fact, BMS. We learned in redirect that
23 this was an issue.

24 So our requirement is that we should disclose
25 two days in advance. We disclosed one day in advance here

1 because it happened yesterday. We didn't know the day
2 before that this was going to be an issue.

3 MR. ROZENDAAL: Your Honor, I'm not objecting on
4 the basis of timeliness. I'm explaining that the reason why
5 this dispute didn't surface earlier is because there was a
6 late disclosure.

7 THE COURT: Right.

8 MR. GROOMBRIDGE: And, Your Honor, frankly, the
9 way we see the evidence is this, right, the burden is on
10 them. It's clear and convincing evidence. If the evidence
11 is, in fact, as we heard it, to be at best equivocal -- I
12 mean, on cross-examination Dr. Perni said unequivocally yes,
13 this was in the public domain, the BMS process was in the
14 public domain before the priority date of this patent. On
15 redirect examination he said, well, maybe I'm not so sure
16 what the date was, right.

17 That, in our view, couldn't possibly be clear
18 and convincing evidence, and I'm not sure that it's even --
19 you know, it requires it. But we thought we would rather
20 have clarity around this issue because if it turns into a
21 dispute in the posttrial briefing, right, we 'd just rather
22 have the record, the facts laid out so Your Honor has them.

23 And that is what prompted us to say, let's, you
24 know, let's just make this clear, right.

25 Now, in our view, if there be a lack of clarity,

1 that then inures to our benefit because the burden is on
2 them, it's clear and convincing standard. So we are -- we
3 could simply say, look, I mean, if we're not going to get
4 into this, then what we have at most is testimony that at
5 some point the BMS process became public and we don't know
6 when. And that can't possibly support an assertion --

7 THE COURT: Except their theory is not, as I
8 understand it, the BMS procedure became public. Their
9 theory is that -- well, it's that it didn't become public.
10 That's the problem.

11 MR. GROOMBRIDGE: Exactly, is that it didn't
12 become public and that BMS gave it -- got it to Vanda,
13 right, and that the reason that they are inventors is
14 because of this important piece of nonpublic information
15 that they created.

16 MR. ROZENDAAL: But, Your Honor, the law is
17 clear if they got it from our inventors, quite apart from
18 the fact that they --

19 THE COURT: I don't know who the "they" is.

20 MR. ROZENDAAL: Sorry. If Vanda received the
21 relevant process information from BMS, in confidential
22 circumstances so that it was not public and then that later
23 became public, that doesn't detract from the fact that
24 Vanda's -- the origin of the idea for Vanda was the
25 confidential disclosure from BMS which, I think, requires

1 BMS to be credited with the contribution to the invention
2 because the conception came from BMS.

3 Essentially the BMS people were de facto
4 coinventors because the Vanda people took their process and
5 evaluated it. You know, you can imagine if it was in a
6 single company, if BMS had kept it, right, the process
7 people would develop it, they'd say, here's the product, why
8 don't you, you know, analytical chemists go find out if
9 there's any impurities in here, and oh, while you're at it,
10 why don't you tell us what they are, that would be all
11 together.

12 And the same thing happened here. It's just
13 that in the interim, this product was transferred to Vanda
14 under confidential circumstances. And under those
15 circumstances where Vanda is drawing on the prior work done
16 by BMS, coinventorship status is warranted. Quite apart
17 from the fact of whether that later became public.

18 Now, of course if Your Honor construes the
19 claims so that it has to be done in one step, then this is
20 not an issue that we'll have to decide.

21 THE COURT: Yeah, but I might want to address
22 multiple issues. I mean, that's always a discretionary call
23 on the judge's part what to do.

24 MR. ROZENDAAL: Of course. I just wanted to
25 observe that this --

1 THE COURT: Right. I mean, but what it also
2 sounds -- is it basically uncontested that there was this
3 disclosure, or is your expert going to say, that wasn't a
4 disclosure of BMS's process?

5 MR. ROZENDAAL: I don't know exactly what our
6 expert would say about it if he were to be asked about it,
7 Your Honor.

8 THE COURT: Did you bring out on direct that BMS
9 had not disclosed this publically?

10 MR. ROZENDAAL: I don't think that was a
11 specific question that was asked.

12 THE COURT: Mr. Groombridge, do you recall?

13 MR. GROOMBRIDGE: I believe they did not, Your
14 Honor. They did not touch this at all.

15 THE COURT: See, and then -- and then you
16 brought out on cross, you raised the issue for the first
17 time on cross, and the witness said, essentially, I don't
18 know when.

19 MR. GROOMBRIDGE: Well, I think on cross the
20 witness said, yes, it was publically available. The witness
21 said on direct, it's my opinion that the BMS people were
22 inventors. But --

23 THE COURT: Right. And then you brought out on
24 cross that BMS had publically disclosed this information
25 before the priority date.

1 MR. GROOMBRIDGE: Correct.

2 THE COURT: Unequivocally.

3 MR. GROOMBRIDGE: Unequivocally.

4 THE COURT: I don't remember it, but --

5 MR. GROOMBRIDGE: Right.

6 MR. ROZENDAAL: But then when he was asked, why
7 did you say that? He said, well, I think that at some point
8 the IND becomes public but I don't know if that happened or
9 when it happened, essentially, in substance, on redirect.

10 THE COURT: Okay. Right.

11 MR. ROZENDAAL: So what he did not say is, oh,
12 there's this prior art reference that reveals the process,
13 right. He pointed to a regulatory document that he said he
14 thought at some time might have become public.

15 MR. GROOMBRIDGE: But, Your Honor, at his
16 deposition --

17 THE COURT: I know. But, I mean, in fairness,
18 we don't have sur -- we don't have re-re -- or recross,
19 right. I mean, that's -- and if that would have been
20 occasioned, but that's the way the system works and that's
21 the way trial is set up.

22 MR. GROOMBRIDGE: Exactly, Your Honor, but had
23 he said to me on cross, I think that it did not become
24 public, I would have impeached with the deposition, but he
25 candidly said it did.

1 THE COURT: Right. Well, then impeachment would
2 have been allowed to use for substantive purposes or just to
3 attack his credibility?

4 MR. GROOMBRIDGE: I think just to attack his
5 credibility.

6 THE COURT: So you got it even better.

7 MR. GROOMBRIDGE: Exactly, yeah.

8 THE COURT: Right. Well --

9 MR. GROOMBRIDGE: And --

10 THE COURT: Go ahead.

11 MR. GROOMBRIDGE: One other point is had we gone
12 down that path --

13 THE COURT: What do you mean had you gone
14 down -- what path?

15 MR. GROOMBRIDGE: Well, so, for example, on
16 cross, if Dr. Perni had said, no, it was not made public --

17 THE COURT: Yeah, but he didn't.

18 MR. GROOMBRIDGE: Yeah, no. But at that point,
19 we could have offered the documents and said, here it is.
20 It's because he simply said yes, I agree with that, there
21 was no need to get into details about it.

22 THE COURT: Yeah, this is the thing about a
23 bench trial, right. I mean, Mr. Rozendaal isn't
24 contradicting as a factual matter anything he's saying. So
25 how does it not influence me, right? It's impossible to

1 remove this from my brain. All right?

2 MR. GROOMBRIDGE: Yes.

3 THE COURT: It makes me inclined to just say
4 since you admit it was not disclosed in the expert's report,
5 it's a Rule 26 issue and it can't come in. And Mr. Stone is
6 demonstratively upset about that.

7 MR. STONE: I don't think we haven't admitted it
8 was not disclosed in his expert report, I was basically
9 trying to figure this out.

10 And the reason for that, Your Honor, our
11 colleague, Ms. Young, who will be doing the examination, and
12 the witness, happened to not be here; they are working at
13 the office this morning. So I was trying to get the answer
14 to this question.

15 THE COURT: Okay.

16 MR. STONE: The fact that this prior art
17 reference discloses the process, I believe, is in the expert
18 report. It is not disclosed in the context of, did BMS
19 invent those steps because that didn't become an issue until
20 yesterday.

21 THE COURT: Got it, got it.

22 MR. STONE: But the fact of the document and it
23 being the process I believe is in the expert report.

24 THE COURT: All right. Well, so listen. If
25 it's in the expert report, right, it comes in.

1 Mr. Rozendaal, right?

2 MR. ROZENDAAL: Well, it's in the expert report
3 disclosed in the context of a different legal argument about
4 a different --

5 THE COURT: It could be, but if what's in the
6 report is there's this article, and the article discloses
7 BMS's process, then it's -- it doesn't matter what context
8 it's in.

9 MR. ROZENDAAL: Can I just have one second, Your
10 Honor.

11 It does not say it's BMS's process.

12 THE COURT: Well, we're arguing. But I said if.
13 In other words, my point would be, why don't we wait and
14 see? Let's get -- they get to look at the report and you
15 get to look at the report. Because if the report states
16 there's an article and the article disclosed BMS's
17 process --

18 MR. ROZENDAAL: It's not going to say that, Your
19 Honor.

20 THE COURT: All right. Well -- but I said if,
21 then it comes in.

22 MR. ROZENDAAL: Right.

23 MR. STONE: I think --

24 THE COURT: And if it doesn't say that, we'll
25 have to figure it out.

1 MR. STONE: I think the issue is that it says
2 there's an article that discloses the process. What was
3 later admitted in deposition is, oh, that's a BMS article.
4 The article was being discussed for was the process known.
5 It was actually their argument that the process was known.

6 At deposition, their witness admitted yes,
7 that's a BMS -- the authors of this article work at BMS;
8 yes, it's a BMS article. On redirect, he suddenly didn't
9 remember when that had happened, which is why we want to
10 simply offer it to say, here's the answer. Here's the
11 article, these are BMS people, that's the date.

12 MR. ROZENDAAL: That is a mischaracterization of
13 his testimony yesterday, Your Honor. What he said was, I
14 thought it was public because of some regulatory filing
15 which may or may not have become public some day, which has
16 nothing to do with this article.

17 So the suggestion that he was somehow clarifying
18 his redirect testimony I don't think is accurate.

19 THE COURT: Okay.

20 MR. GROOMBRIDGE: Your Honor, would it be
21 helpful if both sides looked at the expert reports and
22 see if we can --

23 THE COURT: Yeah. When is this person going to
24 testify?

25 MR. STONE: He's the last witness of the day.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. GROOMBRIDGE: He's the last witness of the
2 day --

3 THE COURT: All right. So yeah, why don't we
4 look at it.

5 MR. GROOMBRIDGE: And he's several hours off in
6 the future.

7 THE COURT: Okay. All right.

8 MR. GROOMBRIDGE: Thank you, Your Honor.

9 THE COURT: All right. Hold up one second.
10 Go ahead then. Thank you.

11 MR. MILLIKEN: Good morning, Your Honor.
12 Defendants call their next witness, Dr. Jonathan Emens.

13 And, Your Honor, while they are getting set up,
14 I understand that the parties have agreed not to dispute the
15 qualifications of the experts in this case, and so we would
16 tender Dr. Emens as an expert in the field of the diagnosis
17 and treatment of sleep disorders, including the fields of
18 circadian physiology, circadian rhythm sleep disorders, and
19 Non-24 Hour Sleep/Wake Disorder.

20 JONATHAN EMENS, having been called on the part
21 and behalf of the Defendant as a witness, being first duly
22 sworn under oath, testified as follows:

23 DIRECT EXAMINATION

24 BY MR. MILLIKEN:

25 Q. Good morning, Dr. Emens. Could you please introduce

DIRECT EXAMINATION - JONATHAN EMENS

1 yourself to the Court.

2 A. Yeah, my name is Dr. Jonathan Emens.

3 Q. And Dr. Emens, have you prepared some demonstratives
4 to assist with your testimony today?

5 A. I have.

6 Q. And can you explain what's displayed here on DTX-5.2?

7 A. Just a general overview of what I hope to cover in my
8 testimony, just a quick overview of my credentials, summary
9 of my opinions, briefing on the state of the art, and then
10 my opinions on the invalidity.

11 Q. Okay. And so first, just a bit on your credentials.

12 What are your current positions?

13 A. I'm currently the Deputy Director of Mental Health at
14 the VA Portland Health Care System. I'm also an associate
15 professor in the pharma-psychiatry in our academic affiliate
16 Oregon Health and Science University and also Department of
17 Medicine at OHSU. So I do teaching of fellows and
18 residents. And I also work as a physician in the VA
19 treating sleep disorders.

20 Q. And could you briefly summarize your educational
21 background, please.

22 A. I got my undergraduate degree at Oberlin College.
23 Medical school at the University of Massachusetts. And then
24 I did my internship and psychiatric residency at Oregon
25 Health & Science University.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. And are you a member of any professional
2 organizations?

3 A. Yes. I'm a distinguished fellow in the American
4 Academy -- sorry, the American Psychiatric Association. I'm
5 a member of the Oregon Physicians Psychiatric Association
6 [sic]. I'm also a fellow in the American Academy of Sleep
7 Medicine and a member of the Sleep Research Society.

8 Q. And do you have any research experience in the field
9 of circadian physiology?

10 A. I do.

11 Q. Could you briefly summarize that experience?

12 A. Yeah, so I have over 30 years of experience and
13 research in circadian physiology in Non-24. So that started
14 in laboratory of Dr. Charles Czeisler about 30 years ago at
15 Brigham and Women's Hospital at Harvard Medical School.

16 I then went to Oregon where I worked in the
17 laboratory of Dr. Alfred Lewy and Dr. Robert Sack, who were
18 the first -- who showed that melatonin could entrain
19 individuals with Non-24. And they also -- Lewy invented the
20 dim light melatonin onset that we've heard a little bit so
21 far in this case.

22 I was on the task force for the treatment of
23 circadian rhythm sleep disorders by the American Academy of
24 Sleep Medicine. And I have and continue to do federally
25 funded research on circadian physiology and circadian rhythm

DIRECT EXAMINATION - JONATHAN EMENS

1 sleep disorders including Non-24.

2 Q. And just to be clear, you mentioned your work
3 Dr. Charles Czeisler. You understand that he's offering
4 some opinions in this case also on behalf of Vanda, correct?

5 A. I do.

6 Q. And have you published any articles or other written
7 materials on the topics of circadian rhythm sleep disorders
8 and Non-24, specifically?

9 A. Yeah, so I've published over 20 research articles on
10 Non-24 and circadian physiology in general. And I'm also
11 the author of the American Academy of Sleep Medicine's
12 practice parameters for the treatment of Non-24.

13 Q. Okay. Thank you, Dr. Emens.

14 At a high level, what issues were you asked to
15 analyze as a part of your work on this case?

16 A. So I was asked to assess the validity of patents to
17 treat patients with the drug tasimelteon.

18 Q. And have you formed any opinions on the validity of
19 those patents?

20 A. I have.

21 Q. And have you prepared a slide summarizing those
22 opinions?

23 A. I have.

24 Q. And I'm going to get to the details of your opinions
25 in a bit, but first just a few preliminaries. What, if

DIRECT EXAMINATION - JONATHAN EMENS

1 anything, did you review in forming your opinions on the
2 validity of these patents?

3 A. So, I looked at the relevant patents, the prosecution
4 histories, of course, the literature in the field, other
5 expert reports. And in particular, Dr. Greenblatt's
6 opinions on drug-drug interactions. And then I have also
7 been in the court so I have used the testimony of other
8 people in this case.

9 Q. And did you rely on Dr. Greenblatt's opinions in
10 forming your own opinions regarding the obviousness of the
11 method of treatment patents that have to do with drug-drug
12 interactions?

13 A. I did.

14 Q. And why did you rely on Dr. Greenblatt's opinions in
15 that regard?

16 A. So he's an expert in pharmacology and in particular
17 the cytochrome P450 enzyme drug interaction that we have
18 heard a lot about that. So I relied on him about those
19 drug-drug interactions as it relates to tasimelteon.

20 Q. Thank you. Let's talk a bit now about the patents.
21 Could you tell us, just at a high level, what the first
22 three patents the RE '604, the '829 and the '910 patent
23 cover?

24 A. Yeah. So they cover a method of treating the
25 circadian rhythm sleep disorder Non-24 by giving

DIRECT EXAMINATION - JONATHAN EMENS

1 tasimelteon. And the '829 and the '910 patent also are a
2 method of treating Non-24 with tasimelteon but include the
3 provision of discontinuing certain CYP, either inducers or
4 inhibitors, before you start the tasimelteon.

5 Q. And what about the fourth patent that you analyzed,
6 the '487?

7 A. So that, again, is a method of treating Non-24 with
8 tasimelteon, but has a stipulation of doing so without food.

9 Q. And in forming your opinions about the validity of
10 the patents, did you use the viewpoints of a person of
11 ordinary skill in the art as of January 2012?

12 A. I did.

13 Q. And you've prepared a slide, DDX-5.9, showing those
14 qualifications?

15 A. Yes.

16 Q. And you are aware Dr. Czeisler has offered a somewhat
17 different definition of a person of ordinary skill in the
18 art?

19 A. I am.

20 Q. Do you qualify as a person of skill in the art under
21 both your own definition and Dr. Czeisler's definition?

22 A. I do.

23 Q. Great. I'd like now to talk a little bit about the
24 state of the art as of January 2012.

25 So, first, a little bit of terminology. We've

DIRECT EXAMINATION - JONATHAN EMENS

1 heard some about these terms already this week, but could
2 you briefly describe what a circadian rhythm is.

3 A. Yeah, so very simply, a circadian rhythm is a
4 spontaneously generated, meaning it's an endogenous rhythm,
5 in a wide variety of physiological and behavioral rhythms.

6 So if you think about your heart generates a
7 beat-to-beat rhythm of a periodicity of about a second, you
8 also have a pacemaker in your brain that generates a rhythm
9 with a periodicity of about 24 hours.

10 Q. And could you give us some examples of circadian
11 rhythms.

12 A. Yeah. So we've heard about some of these, the
13 hormones cortisol and melatonin have an endogenous circadian
14 rhythm. Core body temperature does. And most importantly
15 for this case, the propensity for sleep and wakefulness has
16 an endogenous rhythm too.

17 Q. Okay. And what is a circadian rhythm sleep disorder?

18 A. Again, I think, very simply, a circadian rhythm sleep
19 disorder is just a mismatch between these endogenous drives
20 for sleep and wakefulness and the desire or required times
21 for sleep and wakefulness.

22 Q. And could you give us some examples of circadian
23 rhythm sleep disorders.

24 A. Yeah. So I have up on the slide here things like jet
25 lag, which I think most of us are familiar, as well as

DIRECT EXAMINATION - JONATHAN EMENS

1 Non-24, which is the issue at hand.

2 Q. And have you prepared a demonstrative with sort of a
3 schematic explaining some of these disorders?

4 A. I have.

5 Q. And could you explain to the Court, please, what the
6 bars on this schematic represent.

7 A. Yeah, so these represent the circadian drive for
8 sleep.

9 Q. Do they represent the actual timing of sleep?

10 A. No.

11 Q. Why is that?

12 A. Well, because we can attempt to be awake or be asleep
13 in opposition to our circadian drive for wake and sleep.

14 Q. So just to recap what you've been saying, is it fair
15 to say that people with circadian rhythm disorders are
16 presumed to have circadian rhythms that are misaligned for
17 their desired times for sleep and wakefulness and other
18 things?

19 A. Yes, that's correct.

20 Q. So we have here at the bottom Non-24. Can you
21 explain briefly what Non-24 is.

22 A. Yeah. So Non-24 in totally blind individuals is a
23 result of not getting that resetting effect on their 24-hour
24 biological clock from light. They've lost that light input,
25 so to speak, into that pacemaker or clock in their brain.

DIRECT EXAMINATION - JONATHAN EMENS

1 And as a result, they can't stay synchronized
2 or, as we've heard, entrained in the 24-hour day. And so,
3 for example, if I had a biological day length of 24 hours
4 and 30 minutes long, then I would have this tendency for all
5 of these rhythms that are under the control of the clock,
6 sleep, wake propensity, all these hormones, core body
7 temperature, would all have this tendency to drift about
8 30 minutes later on average every day.

9 And so that's what we see at the bottom of this
10 slide, this progressive drifting to the right and this
11 propensity for sleep. And, so, again, that's what the bars
12 are representing.

13 Q. And in the literature on this topic, has Non-24 been
14 referred to by another name?

15 A. Yes, free-running disorder.

16 Q. So as of January 2012, did researchers and clinicians
17 in this field know how to treat circadian rhythm sleep
18 disorders?

19 A. They did.

20 Q. And how were such disorders treated?

21 A. So to treat a circadian rhythm sleep disorder, you
22 really have two choices. You can give a sedative hypnotic
23 medication to help people sleep when their body is trying to
24 wake them up, and you can give them an alerting medication
25 when their endogenous rhythm for wakefulness is trying to

DIRECT EXAMINATION - JONATHAN EMENS

1 wake them up.

2 And your second option is to give an agent to
3 reset the timing of the biological clock.

4 Q. If you chose the option to giving an agent to reset
5 the timing of a biological clock, how does that treat the
6 circadian rhythm sleep disorder?

7 A. So using the example of Non-24 that I gave before, if
8 my timing of my clock is moving about 30 minutes later every
9 day, we would call that a phase delay. It's a tendency to
10 move to a later time. And so by giving an agent that would
11 reset the clock, it would shift the clock, say, an
12 equivalent 30 minutes earlier to counteract that tendency to
13 move later.

14 And then that result is I wouldn't drift at all.
15 And so that phase shift, that resetting of the clock, is the
16 mechanism by which I have achieved this entrainment or this
17 synchronization.

18 Q. Before January 2012, were there drugs that were known
19 to reset the biological clock?

20 A. There were.

21 Q. Can you give us some examples.

22 A. Tasimelteon and melatonin.

23 Q. And did those of skill in the art know the biological
24 mechanism by which this resetting effect happens?

25 A. They did.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. And could you explain that mechanism, please?

2 A. Yeah. They bind to the melatonin 1 and melatonin 2
3 receptors that are often abbreviated as MT 1 and MT 2.

4 Q. And you mentioned earlier you could treat circadian
5 rhythm disorders by either, on the one hand administering
6 sedatives, hypnotics, on the other hand administering a
7 resetting agent.

8 Are there any drugs that do both?

9 A. Certainly, yes, there are.

10 Q. Could you give us some examples.

11 A. Yeah, so tasimelteon would be an example of such a
12 drug.

13 Q. Okay. Dr. Emens, you've read Dr. Czeisler's and
14 Dr. Lockley's expert reports in this case, right?

15 A. I have.

16 Q. And are you aware that, in their opinion, the prior
17 art is extremely conflicting and confusing and points in
18 different directions when it comes to sort of what was known
19 about how to treat Non-24 with melatonin and tasimelteon?

20 A. I am.

21 Q. And do you agree with their position on that?

22 A. I do not. I strongly disagree with that position. I
23 think the prior art was very clear that melatonin was an
24 accepted and effective way of entraining the biological
25 clock in people with Non-24.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. And do you understand that you're not going to have
2 an opportunity to take the stand to respond to Dr. Czeisler
3 and Dr. Lockley about the state of the art after they have
4 testified?

5 A. I do.

6 Q. Okay. And --

7 THE COURT: And why is that?

8 MR. MILLIKEN: Because according to the order of
9 proof in the pretrial order, to the extent Dr. Emens is
10 called as part of sort of a reply case, it would be limited
11 to the topic of secondary considerations.

12 THE COURT: Are the plaintiffs similarly limited
13 when it comes to -- they're not going to have any
14 noninfringement, for instance, rebuttal; is that right?

15 MR. MILLIKEN: I don't believe that there's any
16 opportunity for, in effect, reply testimony on infringement.

17 MR. GROOMBRIDGE: That's the order of proof,
18 that's correct.

19 THE COURT: Okay. You all agreed to it? All
20 right.

21 BY MR. MILLIKEN:

22 Q. So I'd like the Court to hear why you disagree with
23 Dr. Czeisler and Dr. Lockley on these issues.

24 Have you prepared a couple of timelines showing
25 the development of melatonin and tasimelteon, respectively,

DIRECT EXAMINATION - JONATHAN EMENS

1 for the treatment of circadian rhythm disorders and Non-24,
2 specifically?

3 A. I have.

4 Q. Okay.

5 MR. MILLIKEN: Your Honor, I want to preview
6 that these timelines contain a lot of information and we're
7 going to be introducing quite a bit of evidence, but this is
8 really critically important material for our obviousness
9 combinations. And I'm going to move through it efficiently.
10 I just wanted the Court to be aware.

11 BY MR. MILLIKEN:

12 Q. All right. Let's start with a melatonin timeline.

13 Just to orient us, at what point in time did
14 those in this field start studying biological resetting
15 effects of melatonin?

16 A. So in the early 1980s. So 1983, actually, was the
17 first demonstration in animals that melatonin could reset
18 the biological -- the 24-hour biological clock and cause
19 entrainment.

20 Q. All right. Let's look at the first reference
21 displayed on your timeline.

22 Could you turn, please, to JTX-139 in your
23 binder.

24 A. Yes, I'm there.

25 Q. And do you recognize this document?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. I do.

2 Q. And what is JTX-139?

3 A. So this is a research paper by Deacon and Arendt from
4 1995.

5 Q. And did you rely on this paper in forming your
6 opinions?

7 A. I did.

8 MR. MILLIKEN: Your Honor, I move JTX-139 into
9 evidence.

10 MR. GROOMBRIDGE: No objection.

11 THE COURT: All right. It's admitted.

12 (JTX-139 admitted into evidence.)

13 BY MR. MILLIKEN:

14 Q. Dr. Emens, what is the subject of the Deacon and
15 Arendt paper?

16 A. It's about the phase shifting or resetting of the
17 clock effects of melatonin.

18 Q. And what do Deacon and Arendt conclude about those
19 effects?

20 A. So they conclude two things. One, that melatonin is
21 able to phase shift or reset the circadian rhythm pacemaker.
22 And, two, it would, therefore, be useful in the treatment of
23 circadian rhythm sleep disorders such as Non-24.

24 Q. Okay. Let's move to the next reference. Could you
25 turn in your binder, please, to JTX-147.

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yes, I'm there.

2 Q. Do you recognize this document?

3 A. I do.

4 Q. And what is this?

5 A. This is a research paper from -- by Lockley and
6 colleagues from the year 2000.

7 Q. And did you rely on this paper in forming your
8 opinions?

9 A. I did.

10 MR. MILLIKEN: Your Honor, I move JTX-147 into
11 evidence.

12 MR. GROOMBRIDGE: No objection.

13 THE COURT: It's admitted.

14 (JTX-147 admitted into evidence.)

15 BY MR. MILLIKEN:

16 Q. What year was the Lockley paper published?

17 A. 2000.

18 Q. And what was the subject of this study?

19 A. So this was a study, again, administering melatonin
20 to individuals with Non-24. And it demonstrated that it
21 could entrain them or, again, synchronize these patients to
22 the 24-hour day.

23 Q. Okay. Let's move now to the next reference. Could
24 you turn in your binder to JTX-148, which I think should be
25 the next document.

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yes.

2 Q. Do you recognize this?

3 A. Yes, I do.

4 Q. And what is this?

5 A. So this is a paper by Robert Sack and colleagues in
6 the New England Journal of Medicine.

7 Q. And did you rely on this paper in forming your
8 opinion?

9 A. I did, indeed.

10 MR. MILLIKEN: Your Honor, I move JTX-148 into
11 evidence.

12 MR. GROOMBRIDGE: No objection.

13 THE COURT: All right. It's admitted.

14 (JTX-148 admitted into evidence.)

15 BY MR. MILLIKEN:

16 Q. And what year was the Sack paper published?

17 A. Also in 2000.

18 Q. Could you please summarize the results in the Sack
19 paper.

20 A. Yes. This was a very exciting paper for us in the
21 field. Bob Sack and Al Lewy showed, again, that you could
22 administer melatonin to individuals with Non-24, reset their
23 clock and successfully entrain them to the 24-hour day.

24 And so its publication in the New England
25 Journal of Medicine really highlighted the significance of

DIRECT EXAMINATION - JONATHAN EMENS

1 that finding.

2 Q. Thank you, Dr. Emens. I'd now like to move to a
3 series of articles on which you're listed as an author. And
4 I'd like to consider these in a group, but let's first
5 quickly go through them individually.

6 Could you turn in your binder to DTX-154.

7 A. Yes.

8 Q. Do you recognize DTX-154?

9 A. I do.

10 Q. And what is it?

11 A. It's a paper by Lewy et al.

12 Q. From what year?

13 A. 2001.

14 Q. Could you now turn to JTX-123.

15 A. Yes, I am there.

16 Q. And do you recognize this document?

17 A. I do.

18 Q. What is it?

19 A. It's a paper by Lewy and Emens et al from 2002.

20 Q. And if you could turn to DTX-155.

21 A. Yes, I am there.

22 Q. Do you recognize this document?

23 A. I do.

24 Q. What is it?

25 A. It's a paper by Lewy and Emens et al from 2004.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. And, finally, if you could turn to DTX-156.

2 A. Yes, I'm there.

3 Q. And do you recognize this document?

4 A. I do.

5 Q. What is it?

6 A. So this is, again, a paper by Lewy and Emens et al
7 from the year 2005.

8 Q. And did you rely on these four papers in forming your
9 opinions?

10 A. I did.

11 MR. MILLIKEN: Your Honor, I move DTX-154,
12 DTX-155, DTX-156 and JTX-153 into evidence.

13 MR. GROOMBRIDGE: No objection.

14 THE COURT: All right. They're admitted.

15 (JTX-DTX-154 admitted into evidence.)

16 (JTX-155 admitted into evidence.)

17 (JTX-156 admitted into evidence.)

18 (JTX-153 admitted into evidence.)

19 BY MR. MILLIKEN:

20 Q. Could you describe at a high level what these four
21 Lewy papers are about, Dr. Emens.

22 A. Yeah, so these are really about refining our
23 treatment of Non-24 with melatonin treatment. And,
24 specifically, a lot around optimization of dose.

25 So, in essence, one of the main things we

DIRECT EXAMINATION - JONATHAN EMENS

1 discovered was that there was an optimal therapeutic window
2 for administering melatonin. So, obviously, if you give too
3 low a dose, your chances of being successful in entraining
4 goes down. And also, if you give too high a dose your
5 chance of being successful was also dramatically reduced.
6 So there was a therapeutic window.

7 And, in fact, what was interesting in the Sack
8 2000 paper that I called out especially, one of the patients
9 they were not able to entrain, and by optimizing that dose,
10 we were actually able to entrain that seventh individual.

11 Q. And what was, sort of, the overall takeaway from
12 these four -- these four papers on which Dr. Lewy is the
13 lead author?

14 A. Yeah, so the overall conclusion was that melatonin
15 can successfully cause sufficient phase shifts to entrain
16 individuals with Non-24 conclusively.

17 Q. Thank you. Let's now move to the --

18 THE COURT: You said sufficient what?

19 THE WITNESS: Phase shifts.

20 THE COURT: Okay. I just wanted to make sure we
21 had it.

22 THE WITNESS: Sorry.

23 BY MR. MILLIKEN:

24 Q. Let's now move to the next item in the timeline.
25 Could you turn in your binder please to JTX-146.

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yes. Yes I'm there.

2 Q. And do you recognize this document?

3 A. I do.

4 Q. What is this?

5 A. So this is a research paper by Hack.

6 Q. And did you rely on Hack in forming your opinions?

7 A. I did.

8 MR. MILLIKEN: Your Honor, I move JTX-146 into
9 evidence.

10 MR. GROOMBRIDGE: No objection, Your Honor.

11 THE COURT: All right, it's admitted.

12 (JTX-146 admitted into evidence.)

13 BY MR. MILLIKEN:

14 Q. What year was the Hack study published?

15 A. 2003.

16 Q. And what was Hack studying?

17 A. So they were using the a low dose formulation of
18 melatonin like we had, 0.5 milligrams of melatonin, to,
19 again, cause entrainment in individuals, blind individuals
20 with Non-24.

21 Q. And what did Hack conclude about administering
22 0.5 milligrams melatonin to blind individuals with Non-24?

23 A. So, first, they said this will be effective in
24 causing entrainment. And, therefore, they thought it would
25 be a good treatment for Non-24 because its treating and

DIRECT EXAMINATION - JONATHAN EMENS

1 correcting, as they say here, highlighted the underlying
2 circadian disorder itself.

3 Q. All right. Let's move now to the next item in the
4 timeline. Could you turn, please, to DTX-39 in your binder.

5 A. Yes, I'm there.

6 Q. And do you recognize this document?

7 A. I do.

8 Q. What is it?

9 A. So this is a review article by Skene and Arendt from
10 the year 2007.

11 Q. And did you rely on this paper in forming your
12 opinions?

13 A. I did.

14 MR. MILLIKEN: Your Honor, I move DTX-39 into
15 evidence.

16 MR. GROOMBRIDGE: No objection.

17 THE COURT: All right. It's admitted.

18 (JTX-39 admitted into evidence.)

19 BY MR. MILLIKEN:

20 Q. Dr. Emens, you mentioned this is a review article.
21 What's it reviewing?

22 A. So it's reviewing all the literature on the use of
23 melatonin to treat Non-24, circadian rhythm sleep disorders;
24 and the blind refers to Non-24.

25 Q. And what does this review article conclude about the

DIRECT EXAMINATION - JONATHAN EMENS

1 treatment of Non-24?

2 A. So I think they are very clear. They say melatonin
3 is the treatment of choice for the treatment of this
4 disorder, for the treatment of Non-24.

5 Q. Okay. Let's go to the last item in the melatonin
6 timeline.

7 Could you turn, please, to JTX-94 in your
8 binder.

9 A. Yes. I'm there.

10 Q. Do you recognize this document?

11 A. I do.

12 Q. And what is JTX-94?

13 A. This is also a review article, written in this case
14 by Ferguson, et al, from the year 2010.

15 Q. And did you rely on this document in forming your
16 opinions?

17 A. I did.

18 MR. MILLIKEN: Your Honor, I move JTX-94 into
19 evidence.

20 MR. GROOMBRIDGE: No objection.

21 THE COURT: It's admitted.

22 (JTX-94 admitted into evidence.)

23 BY MR. MILLIKEN:

24 Q. So you mentioned this is another review article.
25 What's Ferguson reviewing?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. So the melatonin and melatonin agonists more broadly
2 for the treatment of insomnia.

3 Q. And just to confirm, what is a melatonin agonist?

4 A. So it's something that's going to bind to the
5 melatonin receptors we discussed earlier.

6 Q. And what does Ferguson say about melatonin agonists
7 and their use to treat circadian rhythm sleep disorder?

8 A. So they say that melatonin's ability to cause phase
9 shifts is well known, as highlighted up at the top, and they
10 point out that melatonin has been used to treat circadian
11 rhythm sleep disorders. And they say that the other
12 agonists kind of reviewed here also all appear to be
13 effective in the treatment of circadian rhythm sleep
14 disorders.

15 Q. And what does Ferguson conclude about the evidence in
16 regards to the use of melatonin specifically?

17 A. So that melatonin specifically has strong evidence
18 that it should be effective for the treatment of circadian
19 rhythm sleep disorders.

20 Q. So to sum up our melatonin timeline, could you --
21 could you summarize what a person of skill in the art would
22 have known about the use of melatonin to treat Non-24 by
23 January of 2012?

24 A. So they would have been very clear that melatonin is
25 an effective entraining totally blind individuals with

DIRECT EXAMINATION - JONATHAN EMENS

1 Non-24. That would have been very, very clear. And, in
2 fact, the first American Academy of Sleep Medicine practice
3 parameters that are highlighted on the screen there clearly
4 recommended that melatonin and the doses of 0.5 to
5 10 milligrams have been shown to entrain blind people with
6 Non-24, and that's what they recommended.

7 Q. Was there any debate at the time about the optimal
8 dosing and timing of administration of melatonin?

9 A. Sure. I mean, I think there's, even to this day, I
10 suppose, some debate about exactly, precisely what dose you
11 might use within that relatively narrow range. But both
12 then and now there's no doubt and no debate as to whether
13 melatonin is an effective treatment for this disorder.

14 Q. And could you turn, just briefly, in your binder to
15 be DTX-37.

16 A. Yes, I'm there.

17 Q. And is this the American Academy of Sleep Medicine
18 practice parameters that you were just discussing?

19 A. It is.

20 Q. And did you rely on this document in forming your
21 opinions?

22 A. I did.

23 MR. MILLIKEN: Your Honor, I move DTX-37 into
24 evidence.

25 MR. GROOMBRIDGE: No objection.

DIRECT EXAMINATION - JONATHAN EMENS

1 THE COURT: All right. It's admitted.

2 (DTX-37 admitted into evidence.)

3 BY MR. MILLIKEN:

4 Q. All right. Now that we have a timeline for the use
5 of melatonin to treat circadian rhythm sleep disorders, I'd
6 like to do the same thing but for tasimelteon.

7 So to start off with, what is tasimelteon?

8 A. So it's a synthetic melatonin agonist.

9 Q. And when you say "synthetic," what do you mean?

10 A. Manmade.

11 Q. All right. Let's look at the first reference in the
12 timeline, which is already admitted into evidence.

13 Could you turn, please, to JTX-12?

14 A. Yes, I'm there.

15 Q. And do you recognize this document?

16 A. I do.

17 Q. What is it?

18 A. It's a patent issued to Catt.

19 Q. And did you rely on this in forming your opinions?

20 A. I did.

21 Q. We've heard quite a bit about this patent in the last
22 couple of days, so I'll just ask you this: Does Claim 1 of
23 the Catt patent cover tasimelteon?

24 A. Yes.

25 Q. And does Claim 14 of the Catt patent cover methods of

DIRECT EXAMINATION - JONATHAN EMENS

1 using tasimelteon to treat circadian rhythm disorders?

2 A. Yes, as highlighted there, it does.

3 Q. And you're reading from Claim 14, correct?

4 A. Yes, Claim 14.

5 Q. Okay. Let's move to the next document in the
6 timeline. Could you turn, please, to JTX-91.

7 A. Yes, I'm there.

8 Q. Do you recognize this document?

9 A. I do.

10 Q. What is it?

11 A. This is a paper by Vachharajani and colleagues.

12 Q. And did you rely on this paper in forming your
13 opinions?

14 A. I did.

15 MR. MILLIKEN: Your Honor, I move JTX-91 into
16 evidence.

17 MR. GROOMBRIDGE: No objection.

18 THE COURT: It's admitted.

19 (JTX-91 admitted into evidence.)

20 BY MR. MILLIKEN:

21 Q. When was the Vachharajani paper published?

22 A. 2003.

23 Q. And I see it refers here in the title to BMS 214778.
24 What's that?

25 A. Tasimelteon.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. Broadly speaking, what's that paper about?

2 A. So it's study of the pharmacokinetics and metabolism
3 of tasimelteon as the article alludes to.

4 Q. And was that in human or animals?

5 A. So these were animal studies. And in general, what
6 they conclude here, what I have highlighted in the abstract,
7 was that they really concluded that based on the fact that
8 it's acting on the melatonin receptors, they thought this
9 should be useful for the treatment of what they call
10 disruption of circadian rhythms, which would be a circadian
11 rhythm sleep disorder.

12 Q. Thank you. Let's move to the next item.

13 Could you turn, please, to DTX-41.

14 A. Yes, I'm there.

15 Q. And do you recognize this document?

16 A. I do.

17 Q. What is it?

18 A. So this is a patent issued for -- to Vanda.

19 Q. All right. Is it a patent or a patent application?

20 A. Excuse me, patent application.

21 Q. And did you rely on this document in forming your
22 opinions?

23 A. I did.

24 MR. MILLIKEN: Your Honor, I move DTX-41 into
25 evidence.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. GROOMBRIDGE: No objection, Your Honor.

2 THE COURT: It's admitted.

3 (DTX-41 admitted into evidence.)

4 BY MR. MILLIKEN:

5 Q. Who's the applicant on this patent application?

6 A. Vanda Pharmaceuticals.

7 Q. And when was it published?

8 A. 2007.

9 Q. The summary of the Invention section of the '244
10 Publication talks about something called MA-1. Do you see
11 that?

12 A. I do.

13 Q. What's MA-1?

14 A. That's tasimelteon.

15 Q. And at a very high level, what does the '244
16 Publication say about tasimelteon?

17 A. So it says that it will bind to melatonin receptors
18 and has chronobiotic activity; meaning, again, it can reset
19 the time of your clock and cause entrainment. And
20 specifically at doses of about, as we have highlighted
21 there, 20 to 50 milligrams when administered about half an
22 hour before bedtime.

23 Q. And does the '244 Publication say anything about
24 circadian rhythm sleep disorders in particular?

25 A. Yes, it does. So it talks about being administered

DIRECT EXAMINATION - JONATHAN EMENS

1 specifically to treat a circadian rhythm sleep disorder;
2 again, when administered about a half an hour before bedtime
3 in a dosage of 20 milligrams to about 50 milligrams.

4 Q. And you're reading here from the claims of the '244
5 Publication; is that correct?

6 A. I am.

7 Q. If we move to the next item, could you turn, please,
8 to PTX-816, which is already in evidence.

9 A. Yes, I'm there.

10 Q. Do you recognize this document?

11 A. I do.

12 Q. What is it?

13 A. So it's a research paper by Rajarantnam and
14 colleagues from 2009.

15 Q. And did you rely on this document in forming your
16 opinions?

17 A. I did.

18 Q. At a very high level, what does Rajaratnam describe?

19 A. It describes Phase 2 and Phase 3 studies that
20 demonstrate that tasimelteon can reset the timing of the
21 biological clock; again, cause a phase shift, and improve
22 sleep in response to a shifting of five hours of the timing
23 of sleep and wakefulness.

24 Q. What doses of tasimelteon did Rajarantnam study?

25 A. They tried 10, 20, 50, and 100 milligrams.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. And which dose resulted in the biggest phase shift
2 among those four?

3 A. The 100-milligram dose.

4 Q. Would they suggest to a person skilled in the art
5 that lower doses wouldn't be effective in treating circadian
6 rhythm sleep disorders?

7 A. No.

8 Q. Why not?

9 A. Well, you can see in Figure 2, highlighted in green,
10 that the dose of 20 milligrams of tasimelteon caused over an
11 hour shift to an earlier time of the biological clock. So,
12 again, a phase advance shift of over an hour.

13 Q. And would that be enough to treat a disorder like
14 Non-24?

15 A. It would be able to treat anyone with a disorder like
16 Non-24. You would never really need a shift of more than an
17 hour, and so it would be a sufficient shift to treat any
18 individual with Non-24.

19 Q. All right. Let's move to the next item in the
20 timeline.

21 Could you turn, please, to DTX-16?

22 A. Yes, I'm there.

23 Q. Do you recognize this document?

24 A. I do.

25 Q. What is it?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. So, again, this is a review article; in this case by
2 Hardeland from the year 2009.

3 Q. Did you rely on Hardeland in forming your opinions?

4 A. I did.

5 MR. MILLIKEN: Your Honor, I move DTX-16 into
6 evidence.

7 MR. GROOMBRIDGE: No objection.

8 THE COURT: It's admitted.

9 (DTX-16 admitted into evidence.)

10 BY MR. MILLIKEN:

11 Q. Does this Hardeland 2009 article talk about the
12 Rajarantnam studies that we just discussed?

13 A. It does.

14 Q. And what conclusions does Hardeland draw based on its
15 review of the tasimelteon literature?

16 A. So it concludes that, like I have highlighted on the
17 left, tasimelteon can phase shift the circadian clock, and
18 it should be useful in the treatment of circadian rhythm
19 sleep disorders.

20 And Hardeland goes on to conclude that this
21 would be expected based on the fact that it's a melatonergic
22 drug. So Hardeland is not at all surprised that it would be
23 useful in that regard.

24 Q. All right. Thank you, Dr. Emens. Let's move to the
25 next item.

DIRECT EXAMINATION - JONATHAN EMENS

1 Could you turn in your binder, please, to
2 DTX-419.

3 A. Yes, I'm there.

4 Q. Do you recognize this document?

5 A. I do.

6 Q. What is it?

7 A. So this is a web page from clinicaltrials.gov.

8 Q. And what is this web page from clinicaltrials.gov
9 describing?

10 A. It's describing a Phase 3 trial of tasimelteon to
11 treat totally blind individuals with Non-24.

12 MR. MILLIKEN: Your Honor, I move DTX-419 into
13 evidence.

14 MR. GROOMBRIDGE: Your Honor, on this one, we
15 may have an objection.

16 THE COURT: All right.

17 MR. GROOMBRIDGE: The question is, what is it
18 being offered for and specifically whether it's being
19 offered for the truth.

20 And the issue here, Your Honor, is we would have
21 no objection to Dr. Emens testifying about the content of
22 it, but if he intends to testify to the publication of it or
23 if there's going to be an attempt to say that it was
24 published on a particular date, because it says that in the
25 document, we think that's hearsay, we think there's a lack

DIRECT EXAMINATION - JONATHAN EMENS

1 of foundation.

2 And so it really depends on the purpose for
3 which the defendants are offering it.

4 MR. MILLIKEN: Your Honor, I can --

5 THE COURT: Just give me a second.

6 MR. MILLIKEN: I'm sorry.

7 THE COURT: So I guess I'm a little confused by
8 the objection because if there's a dispute about the date of
9 the publication, then there should be a 402 objection. I
10 mean, should -- this should be totally irrelevant unless
11 it's established that it's prior art.

12 MR. GROOMBRIDGE: Correct, Your Honor. And if
13 they intend to offer some other form of evidence proving the
14 date, so be it. But what we would be objecting to is an
15 effort to introduce a document and then have Dr. Emens
16 testify that it's prior art because of the date that it says
17 on its face.

18 THE COURT: So I get that, but, I mean, isn't
19 the --

20 MR. GROOMBRIDGE: And --

21 THE COURT: You said you didn't mind him
22 testifying about the truth of the matter asserted in the
23 document, but it'd be irrelevant unless it's prior art,
24 right?

25 MR. GROOMBRIDGE: That's our view, Your Honor.

DIRECT EXAMINATION - JONATHAN EMENS

1 It would have to be proven to be prior art. And it is
2 irrelevant unless such proof comes. They may have some
3 means by which they think they're going to put that in and I
4 think it up, but absent that, we think it's irrelevant.

5 THE COURT: Mr. Milliken.

6 MR. MILLIKEN: Well, Your Honor, as an initial
7 matter, because this is a federal government website, the
8 Court can take judicial notice of the fact that it says it
9 was posted on July 15th, 2010, but I can also ask Dr. Emens
10 some foundational questions concerning the public
11 availability of the document.

12 THE COURT: All right. Let's do that.

13 MR. GROOMBRIDGE: Again, Your Honor, we would
14 object to that because there's never been anything in his
15 expert report about it and it's an undisclosed opinion.

16 MR. MILLIKEN: That's not -- that's not correct.

17 THE COURT: Don't talk over each other, please.

18 MR. GROOMBRIDGE: I think he has no -- he has no
19 basis to testify to this, and it's not something that was in
20 his expert report.

21 THE COURT: Is the document in his expert
22 report? Is it cited in his expert report?

23 MR. GROOMBRIDGE: It is, and he talks about
24 the -- what it says, right, and he talks about the date on
25 its face, but he doesn't say, and here's why I know it was

DIRECT EXAMINATION - JONATHAN EMENS

1 available publically.

2 THE COURT: Well, I don't know that I have ever
3 seen that in an expert report; have you? Is it in your
4 expert reports? Do they authenticate that they confirm
5 firsthand that the date of an article is the correct date?

6 MR. GROOMBRIDGE: Typically no, Your Honor,
7 because typically the expert is talking merely about what
8 would be the effect of the disclosure of the article.

9 THE COURT: Right.

10 MR. GROOMBRIDGE: If there be a dispute, and in
11 this case there is, about when this was published, then
12 some -- you could imagine another expert saying, or someone
13 saying, here's what I did to verify what --

14 THE COURT: So I can imagine that. Was, during
15 discovery, it articulated by you or your side that there was
16 a dispute about when this particular article was published?

17 MR. GROOMBRIDGE: Yes, Your Honor. We have
18 never conceded that this is prior art. And, in fact, Your
19 Honor may recall --

20 THE COURT: No, I won't recall.

21 MR. GROOMBRIDGE: Well, they went to the Wayback
22 Machine and got a declaration about this. So they were
23 clearly on notice that -- and it's listed in the pretrial
24 order as an open issue because they were -- there was a
25 dispute as to whether this qualifies as prior art. And they

DIRECT EXAMINATION - JONATHAN EMENS

1 would not have obviously went to the Wayback Machine and got
2 a declaration about that.

3 THE COURT: What exactly is a "Wayback Machine"?

4 MR. GROOMBRIDGE: So the Wayback Machine, Your
5 Honor, is an archive of all -- that takes snapshots on the
6 Internet and has a vast -- any website you wanted. If you
7 want to find out if something was on the Internet at a
8 particular time, you could go to them and they will tell
9 you.

10 THE COURT: Is it a private entity that
11 maintains that?

12 MR. GROOMBRIDGE: I think it's a nonprofit, Your
13 Honor. I think it's a private nonprofit based in Texas.
14 And you can go there, and this often comes up in patent
15 cases for all the reasons that one would imagine, and find
16 out when was this on the Internet. And, in fact, we do have
17 such a document here. In our view, it's not early enough to
18 be prior art, but it's not the date that is on the face of
19 this document.

20 THE COURT: Okay.

21 MR. MILLIKEN: Your Honor, Dr. Emens does
22 explain in his expert reports how he knows that this was
23 available in July of 2010. Whether it's necessary or not,
24 it's there.

25 THE COURT: All right. Well, Mr. Groombridge

DIRECT EXAMINATION - JONATHAN EMENS

1 says it isn't. Can you show me the report?

2 MR. MILLIKEN: Sure. May I approach?

3 THE COURT: Sure. Well, why don't you just
4 identify the paragraph so he can look at it while I am
5 looking at it.

6 MR. MILLIKEN: It's Paragraph 84 of the
7 January 31st, 2020, report.

8 THE COURT: All right. For starters, this is a
9 Phase 3 clinical trial conducted -- oh, by Vanda?

10 MR. MILLIKEN: Correct, Your Honor.

11 THE COURT: So this is their clinical trial to
12 get tasimelteon approved.

13 MR. MILLIKEN: It is.

14 THE COURT: Okay.

15 Why don't we excuse the witness, do you mind?
16 And I think we would exclude any other person in the
17 courtroom who might be a factual witness with respect to the
18 authenticity of this document.

19 (Witness was excused and left the courtroom.)

20 THE COURT: So why don't you both look in the
21 courtroom -- just for the record, there's a lot of people in
22 the courtroom. So I'm going to have counsel look because if
23 there is a person in the courtroom, then they could not
24 later on testify with respect to the authenticity of this
25 document if they remain in the courtroom. That includes

DIRECT EXAMINATION - JONATHAN EMENS

1 lawyers, paralegals, or anybody else.

2 All right. Let's establish a couple of
3 predicate facts that would be relevant for me to consider
4 the admissibility of the document at issue.

5 MR. MILLIKEN: Your Honor, might I say one
6 thing?

7 So we discussed this document on a meet and
8 confer, and I understood that they had no objection to its
9 admissibility as evidence. I understand there is an
10 objection about the separate question of whether it
11 qualifies as prior art, but plaintiff's counsel represented
12 to me that there was no objection to the document's
13 admissibility.

14 THE COURT: So, and I kind of agree. I mean,
15 he's already kind of done that in court, right? My point
16 was, what I understood Mr. Groombridge's objection was, hey,
17 we dispute whether this is actually prior art because of the
18 date of its publication, but you can have your witness go
19 testify about it.

20 But see, this is an example where you guys need
21 to do a better job, frankly, of being cognizant of the time
22 that goes on with the Court. It's a public resource that's
23 limited. So I'm not going to allow for the adducement of
24 evidence, testimonial evidence, about some document that may
25 have no bearing on this case. All right?

DIRECT EXAMINATION - JONATHAN EMENS

1 So that's why -- so then I pressed
2 Mr. Groombridge because basically what he's saying, okay,
3 you know what, I'll let Milliken bring this out, but then
4 I'm going to argue this is totally irrelevant, right? So
5 there's really a threshold argument whether under Rule 402
6 this should be admitted at trial at all.

7 Now, it may be well and good for you guys just
8 to bring it in, but I've got limited time. I've tried to
9 impress this upon you. Okay? So we need to resolve it.
10 And even though we're taking all this time, I'd rather
11 resolve it now than when you all brief it, and then three
12 months from now, I have got to figure out what occurred at
13 10:00 on March 30th and remember all this argument and
14 decide whether I should even be considering this.

15 MR. MILLIKEN: Understood.

16 THE COURT: Now, to that end, what I'm trying to
17 figure out is what's really going on here. All right.
18 Because this appears to be, on the face of it -- and, again,
19 for the record, it's DTX- -- what's being designated
20 DTX-419.1, which appears to be a printout from the Internet,
21 from a government Internet site, based on the bottom left
22 corner of the pages of the document, it appears to reflect
23 information about a study that the document says is dated
24 July 13, 2010.

25 On the upper left corner of the first page,

DIRECT EXAMINATION - JONATHAN EMENS

1 actually of all pages of the document -- and for the record,
2 it's a five-page document -- is the date 12/27/2019. And at
3 least on the first page of the top of the document, there
4 are dates ranging from May 21, 2013, to October 15, 2014.
5 So there's a lot of dates in the document.

6 Now, the document, though, on its face
7 identifies Vanda as the sponsor/collaborator of the study.
8 And apparently there's a disclosure, I just saw. Was it
9 paragraph 80- -- what was it?

10 MR. MILLIKEN: 84.

11 THE COURT: -- 84 which cites a document -- at
12 least I'm told it cites a document, I guess there might be a
13 debate about that -- and describes it as reflecting results
14 of a Phase 3 clinical trial event. Right?

15 MR. MILLIKEN: Just to clarify, it's the
16 protocol from the Phase 3 clinical trial. It does not
17 contain the results because the trial had not been conducted
18 yet.

19 THE COURT: Fair enough. So it's the protocol.
20 Thank you for that correction.

21 All right. So a part of me wants to say, well,
22 how is this even in dispute, but I don't know the history of
23 it.

24 MR. MILLIKEN: Your Honor, if I could, and
25 Dr. Emens was going to testify about this, but if I could

DIRECT EXAMINATION - JONATHAN EMENS

1 explain sort of how clinicaltrials.gov works, I think that
2 might shed some light on the question.

3 THE COURT: Sure.

4 MR. MILLIKEN: So companies that are pursuing
5 FDA approval for a drug have to submit their clinical trial
6 protocols and results to clinicaltrials.gov. Clinical trial
7 protocols go through lots of changes as the trial proceeds.

8 THE COURT: And is the website run by FDA?

9 MR. MILLIKEN: I believe it's run -- it is a
10 federal government website. I'm not positive that FDA is
11 the relevant entity, but it is a US government website.

12 THE COURT: Okay.

13 MR. MILLIKEN: What happens is each time the
14 company updates the protocol, they submit the updated
15 version, and clinicaltrials.gov logs these different
16 versions of the protocol in something that is called the
17 history of changes section of the protocol, and it has
18 hyperlinks. So it will say, like, July 15th, 2010, you
19 know, protocol, and then, you know, say September 2010,
20 update XYZ. And you can click on those hyperlinks to see
21 what the protocol looks like on any given date.

22 And so what we're relying on is the very first
23 version of the protocol which says, on the face of the
24 document, that it was submitted on July 13th, 2020 -- or
25 excuse me, 2010 and that it was posted on July 15th, 2010,

DIRECT EXAMINATION - JONATHAN EMENS

1 which is 18 months before the priority date of the patent.

2 THE COURT: All right. Now, how did you find
3 this document?

4 MR. MILLIKEN: It's on the clinicaltrials.gov
5 website.

6 THE COURT: If I went on it right now and I
7 pressed, would I get this document?

8 MR. MILLIKEN: Yes.

9 THE COURT: Okay.

10 MR. MILLIKEN: You would have to go to the
11 History of Changes section and click the July 2010 version,
12 but yes.

13 THE COURT: So if push came to shove, you could
14 have a paralegal get on the stand and say -- well, I'm
15 assuming a paralegal, but I don't know who found the
16 document -- who actually did, do you know? Do you know who
17 actually pulled this document up? Was it Mr. Rozendaal?

18 MR. MILLIKEN: Your Honor, I think that it was
19 probably our cocounsel from Winston & Strawn who are no
20 longer involved in the case, if I had to guess, but I don't
21 know that for sure.

22 THE COURT: Did you have anybody from your firm
23 in the last 24 hours or week do this to see if they could do
24 it?

25 MR. MILLIKEN: I did it last night.

DIRECT EXAMINATION - JONATHAN EMENS

1 THE COURT: Okay. All right.

2 Mr. Groombridge.

3 MR. GROOMBRIDGE: So, Your Honor, first of all,
4 we have no objection to Dr. Emens testifying what's in that
5 Paragraph 84 of his expert report, but that simply says he
6 went and looked at the website. It doesn't say anything
7 about how clinicaltrials.gov operates. And that would be an
8 undisclosed opinion.

9 THE COURT: No, no. See, that's what I'm
10 getting at. That's a fact, right? So if they want to lay
11 the predicate, they're going to be able to, I think, unless
12 you object. See, that's why I want to know what the real
13 dispute is. And I'm a little -- because, frankly, I talked
14 about how I generally like these two firms and you're pretty
15 reasonable people. And so I want to know if there's
16 something going on.

17 Like, in other words, is this just -- and you
18 have every right to do it under the rules, right, but it is
19 a bench trial and I gave you too much time, and the question
20 is -- you think that this document was not posted as of
21 July 15, 2010?

22 MR. GROOMBRIDGE: Oh, we think -- first of all,
23 it says "estimate," and we think it's not clear that it was.

24 They went to the Wayback Machine, and the date
25 that the Wayback Machine gave them was March 7th, 2011.

DIRECT EXAMINATION - JONATHAN EMENS

1 That was the earliest date they could find. And if that's
2 right, it's not prior art.

3 MR. MILLIKEN: Your Honor, could I say one thing
4 about the Wayback Machine?

5 THE COURT: Well, you can. See now, this --
6 this might be a really legitimate question about
7 authentication, which you could have factual testimony. You
8 could have some witness come in and basically say what you
9 just did, that I found the document, and I guess we could go
10 from there.

11 Now I guess maybe we're going to open the door
12 to then we have to have testimony about what the Wayback
13 Machine does and all that.

14 MR. GROOMBRIDGE: Again, Your Honor, we put them
15 on notice in the pretrial phase of the case that we did not
16 concede that this was prior art or that it had been
17 publically available. They did go to the Wayback Machine
18 and got this declaration. They didn't do anything else.
19 They could have gone to clinicaltrials.gov or something like
20 that, but --

21 THE COURT: So they've got a declaration from
22 Wayback.

23 MR. GROOMBRIDGE: Yes.

24 THE COURT: Okay.

25 MR. MILLIKEN: The way the Wayback Machine

DIRECT EXAMINATION - JONATHAN EMENS

1 works, Your Honor, is that it crawls the Internet and it
2 captures websites as they exist at a particular point in
3 time.

4 THE COURT: Right.

5 MR. MILLIKEN: But it doesn't do this
6 constantly. So you might have a capture from X month of one
7 year and then, you know, March of the next year and then
8 September of the next year.

9 It just so happens that the earliest date that
10 the Wayback Machine crawled this particular page was in
11 March of 2011. So that's the earliest Wayback capture that
12 we have.

13 But if you compare that capture to what it says
14 was the operative version as of that date, they match up.

15 THE COURT: Wait, wait. I lost you there.

16 MR. MILLIKEN: Okay, sorry.

17 So there's this record of the history of changes
18 so you can see what the protocol looked like at any given
19 time.

20 THE COURT: Including right now?

21 MR. MILLIKEN: Including right now.

22 THE COURT: So if I went on the website right
23 now, you're saying I could pull up this page.

24 MR. MILLIKEN: Yes.

25 THE COURT: And by "the website," I mean the

DIRECT EXAMINATION - JONATHAN EMENS

1 government website.

2 MR. MILLIKEN: The government website, which we
3 think is self-authenticating because it's a US government
4 website.

5 THE COURT: All right. And what do you say to
6 that, Mr. Groombridge?

7 MR. GROOMBRIDGE: What we say is it's our
8 understanding -- and, again, it's not our burden to prove
9 any of this -- but it's our understanding that it takes
10 clinicaltrials.gov some amount of time to process these
11 things and put them up on the website. And sometimes that
12 happens quickly and sometimes it takes quite a long time.

13 THE COURT: But that would suggest that the last
14 update posted would be the late date; that July 15, 2010,
15 would be the latest it was posted, that it would have come
16 in much earlier.

17 MR. GROOMBRIDGE: The problem is that the
18 content changes over time and you can't be sure that what
19 you're looking at -- as Your Honor sees on this one, it has
20 a whole lot of dates on it, and you cannot --

21 THE COURT: Right. But if I could pull it up on
22 the web right now and I could pull up this exact same sheet,
23 that would suggest that this was posted by the government no
24 later than July 15th of 2010.

25 MR. GROOMBRIDGE: Your Honor, the very version

DIRECT EXAMINATION - JONATHAN EMENS

1 that they're relying on and Dr. Emens proposes to testify
2 about includes, as one of the references, a paper that was
3 published in 2015. This can't be the format in which it
4 existed in 2010.

5 That's at the bottom of page 20 -- 419.3 and
6 carrying up over to the top of 419.4.

7 MR. MILLIKEN: Your Honor, if I --

8 THE COURT: Just a moment. Where is this,
9 Mr. Groombridge?

10 MR. GROOMBRIDGE: On the bottom of 419.3, at the
11 very bottom, there is a section headed References.

12 THE COURT: Oh, yes.

13 MR. GROOMBRIDGE: And then there's a paper which
14 is actually the set and reset studies in the Lancet. And if
15 one turns over to the top of the next page, one can see the
16 date there, 2015.

17 And so whatever this is, it can't be a snapshot
18 of what was on the Internet in 2010.

19 MR. MILLIKEN: Your Honor, presumably the reason
20 for that is that this 2015 paper is what published the
21 results of this clinical trial protocol, and so it's
22 appended to the end of the document. But if you look just
23 above the part that Mr. Groombridge is pointing you to,
24 where it says Contacts/Locations, and it says Central
25 Contacts, this study is not yet recruiting, the study hadn't

DIRECT EXAMINATION - JONATHAN EMENS

1 started yet.

2 This is -- if you click on the July 2010 version
3 on the History of Changes that shows the protocol as it was
4 submitted to the government website -- as it was required to
5 be submitted the government website under FDA regulations,
6 this is the version you get.

7 And if Your Honor logs on to the website right
8 now, you would see the same thing.

9 THE COURT: What you claim is this document
10 labeled DTX-419.1 through 5 was posted on the website of the
11 clinicaltrials.gov site maintained by the government of the
12 United States as of what date?

13 MR. MILLIKEN: It was posted as of July 15th,
14 2010, is what it says. And to be clear --

15 THE COURT: Just hold on. Well, go ahead.

16 MR. MILLIKEN: So that is the content of the
17 protocol. This -- this website was accessed in 2019, as it
18 says, on the top left-hand corner.

19 What I'm saying is --

20 THE COURT: Wait, where are you -- yes. It was
21 accessed in 2019, right.

22 MR. MILLIKEN: Right. So I'm saying that the
23 version that --

24 THE COURT: I just want to -- what you want it
25 to be evidence of is what somebody would have seen had they

DIRECT EXAMINATION - JONATHAN EMENS

1 gone on the website as of July 15, 2010.

2 MR. MILLIKEN: Precisely, Your Honor.

3 THE COURT: Right, that's the point. So that's
4 what you're trying to establish that this reflects.

5 MR. MILLIKEN: Correct.

6 THE COURT: Okay. I just don't like
7 Mr. Groombridge's objection because I don't think, you know,
8 there's any point having anybody testify about this unless
9 it's first established that it's authentic. Under Rule 901:
10 For that to be satisfied, you have to have evidence
11 sufficient to support a finding that the matter in question
12 is what its proponent claims.

13 And you claim this is what a person would have
14 seen on the clinicaltrials.gov website as of July 15, 2010.
15 You haven't done that yet, and you've not tried. So I'll
16 hold you to your burden, and you can try to lay a foundation
17 to do that.

18 I have to say the fact that there appears on its
19 face to be an article that's dated 2015 calls into doubt, in
20 my mind, that this is a fair and accurate reflection of what
21 was on a website as of July 15th, 2010.

22 You can go lay the foundation and see if you can
23 get that in.

24 MR. MILLIKEN: And if I may, Your Honor, in
25 addition to laying the foundation with Dr. Emens, I'd submit

DIRECT EXAMINATION - JONATHAN EMENS

1 that under 902(b)(2), a US government website is a source
2 whose accuracy cannot reasonably be questioned, and the
3 Third Circuit has, in fact --

4 THE COURT: That's not the issue. The issue is
5 whether or not this document reflects what was on that
6 website as of July 15, 2010. That's the issue. So in other
7 words, to satisfy 902, if you had a witness come in -- and
8 I'm sure -- I'll bet you somebody could easily do this, and
9 they could say, I pulled DTX off the Internet, the
10 clinicaltrials.gov Internet on December 27th, 2019, that
11 would come in. There's no question, I think, and I would
12 hold, under Rule 902, that this document could be admitted.
13 It meets 901 because at the top of the page there's the date
14 12/27/2019 -- and I don't even have an objection -- I'm sure
15 I wouldn't have an objection for that -- that this would
16 come in.

17 The question is whether this shows, "this" being
18 DTX-419, what a person would have seen had they gone on the
19 website on July 15th of 2010. That's the challenge.

20 And it is especially challenging because there's
21 an article that's dated 2015 in the document.

22 Now, you might have a person who can explain all
23 this, but it's incumbent upon you to do that in the face of
24 an objection. All right.

25 MR. MILLIKEN: Well, our understanding is that

DIRECT EXAMINATION - JONATHAN EMENS

1 they are not -- they're not objecting to the admissibility
2 of the --

3 THE COURT: Well, he is and he isn't. I mean, I
4 was going to say, I don't think he framed the objection
5 properly, but the effect of what he's objected to does it
6 because he said, I don't think you -- I can consider it
7 for -- as prior art. And he said, the reason why I can't
8 consider it as prior art is because, essentially, there's no
9 proof that this is what someone would have seen on the
10 website on July 15, 2010. That's what he said.

11 And he was okay to let my time be wasted by
12 having your witness opine on, like, the substance of it, but
13 I'm not okay with that.

14 But what his objection really is, is it goes to
15 the authenticity of the document because he's saying it
16 can't be considered for prior art. His whole objection that
17 you can't consider it as prior art is based on the lack of
18 authenticity, I think.

19 MR. GROOMBRIDGE: Correct, Your Honor.

20 THE COURT: I mean, he may not have cited the
21 rule, but -- well, I mean, I'm not making the objection up
22 for him. I know, Mr. Milliken, you're kind of frustrated by
23 that. I mean, I think I've just narrowed the scope of
24 the -- or and cited the relevant federal rule, but he did
25 object on the -- for the substance of what I just

DIRECT EXAMINATION - JONATHAN EMENS

1 articulated, and you've got to show it.

2 And here's the thing. At the end of the day,
3 you'd have to show it to me because I'm not going to have
4 the briefing. I mean, we're going to have all this. Under
5 the way Mr. Groombridge launched the objection, I would have
6 sat here, listened to your witness testify about the content
7 of this, and then we would have gotten to the posttrial
8 briefing and Mr. Groombridge would have said, you can't
9 consider this, it's not prior art. And then we would be,
10 essentially, adjudicating this issue of authenticity.

11 So we may as well adjudicate it now.

12 MR. MILLIKEN: Well, so -- I apologize if this
13 is not responsive to Your Honor's point, but if the
14 objection is essentially one of relevance premised on the
15 document not actually having been publically available
16 before the critical date --

17 THE COURT: No, that's not -- so that's not --
18 well, he didn't object on relevance grounds, although to me
19 it is.

20 MR. MILLIKEN: Well, I understood that to be
21 sort of Your Honor's concern. And if we're talking about
22 the merits of the public availability issue, then I point
23 the Court to the Federal Circuit's decision in *Jazz*
24 *Pharmaceuticals versus Amneal Pharmaceuticals*, 895 F.3d 1347
25 at 1355, and that's from the Federal Circuit in 2018, which

DIRECT EXAMINATION - JONATHAN EMENS

1 recognized the public availability of the document that was
2 posted on a US government website.

3 THE COURT: So, look, I'll tell you what. Does
4 somebody have the case? You can hand it up.

5 But let's just be clear. I'm pretty confident
6 what that case is addressing is a situation where somebody
7 pulled something from a website on a certain date and there
8 was a question as to the authenticity of what was pulled.
9 But I'm going to guess it was not disputed that the question
10 was whether the website, as of the date it was pulled, was
11 authenticated.

12 But let me look. What page is this?

13 MR. MILLIKEN: 1355 is the relevant page.
14 Actually, I apologize, Your Honor.

15 THE COURT: It's all right.

16 MR. MILLIKEN: If you look at 1358 to 1359, it's
17 discussing meeting minutes, transcript, and slides of an
18 open-to-the-public FDA meeting that was published on the
19 FDA's website.

20 THE COURT: Right.

21 MR. MILLIKEN: And it notes that there was --
22 the FDA published a notice in the Federal Register that had
23 a hyperlink to a public FDA website, and it also --

24 THE COURT: Okay. Wait, hold up. Show me in
25 the document where that is.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: I apologize, Your Honor, I gave
2 you my copy.

3 THE COURT: No problem. All right. Hold on.
4 Just give me a second.

5 MR. MILLIKEN: Okay. So if you look at 1358.

6 THE COURT: Yeah.

7 MR. MILLIKEN: There's a paragraph that begins
8 on the left-hand column, and it talks about how -- in this
9 case there was a notice that was published in the Federal
10 Register and it says there was a -- this was an appeal from
11 the board -- a PTAB decision, and it says: There was a
12 board finding that persons of ordinary skill would have been
13 familiar with the Federal Register or they would have been
14 motivated to look at those notices.

15 The second reason that the Court gives in the
16 right hand --

17 THE COURT: Okay. That's irrelevant as far as
18 I'm concerned. I mean, I think that was easily demonstrated
19 here, and I doubt it's going to be contested, that somebody
20 could have gone on this website and pulled this.

21 All right, go ahead.

22 MR. MILLIKEN: The second reason it says is
23 that: The ACA materials were available online for a
24 substantial amount of time before the critical date.

25 And here, that amount of time was two months.

DIRECT EXAMINATION - JONATHAN EMENS

1 Here --

2 THE COURT: Wait, wait. Where -- what are you
3 talking about that period of time was two months?

4 MR. MILLIKEN: So the point that the Federal
5 Circuit is making here is that the document was available
6 online two months before the relevant date that it would
7 need to be publically available to make it prior art.

8 THE COURT: Yeah.

9 MR. MILLIKEN: And my point here is that this
10 government website says it was published on -- or it was
11 posted online in July 2010, which is six months before the
12 date it would have needed to be publically available to
13 qualify as --

14 THE COURT: And I think the question is what was
15 published as of July 15th, 2010. That's the question.

16 Do you believe that -- if you turn to Page 5 of
17 the document, really Page 4, at the very end, do you believe
18 that the citations there, and in particular The Lancet 2015,
19 October 31st article, do you think that was published on the
20 website as of July 15, 2010?

21 MR. MILLIKEN: No, I do not think that the
22 citation --

23 THE COURT: Okay. So then how am I to know what
24 was published before July 15, 2010, and what was published
25 after July 15, 2010, when I look at the document?

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: I think the simplest route, Your
2 Honor, would be for the Court itself to take judicial notice
3 of the clinicaltrials.gov website --

4 THE COURT: I can do that. I'm willing to do
5 that.

6 MR. MILLIKEN: -- and they way the history --
7 the website itself explains how the History of Changes
8 section works. There's literally a tab that you can click
9 where it explains --

10 THE COURT: Then you've got to do all that. I
11 mean, look. I will take judicial notice that there's a
12 clinicaltrials.gov website, and I'm willing to probably take
13 judicial notice of facts about that if you want to show them
14 to me, right.

15 That's not the debate. I think the debate is
16 what in this document was posted and when.

17 And you are purporting to bring this in, as I
18 understood it, as a document that showed what was on the
19 website as of July 15th, 2010, and I excused all the
20 witnesses that might attest to whether that was factually
21 true or not to find out, do I really have a dispute here
22 that's worth me spending time on.

23 And when Mr. Groombridge points to the fact that
24 there's an article dated 2015 in the printout, that suggests
25 to me that there really could be an issue about what was in

DIRECT EXAMINATION - JONATHAN EMENS

1 the public realm, what was on the website as of July 15th,
2 2010.

3 I'm trying to get to the bottom of that.

4 MR. MILLIKEN: Understood, Your Honor. And if I
5 could give just a little bit of background.

6 Originally what we were going to use was a
7 different exhibit, DTX-42, in which we essentially went
8 through all the history of changes, compiled them all
9 together to show how the protocol -- to show the contents of
10 the protocol and then evidentially the study results at each
11 successive point; and that was a much longer document.

12 The plaintiffs objected. They said it's
13 improper, that it's a compilation of a document, but if you
14 want to use just the version that Dr. Emens relied on, which
15 is this expert, just these pages, they said they didn't have
16 an objection to that.

17 And I feel a little bit like I'm being
18 sandbagged here --

19 THE COURT: And you might be.

20 MR. MILLIKEN: -- for that reason because I
21 specifically asked plaintiff's counsel when I move this into
22 evidence, are you going to object, and they said no.

23 THE COURT: Yeah. And so I do have some empathy
24 for you, and it goes back to, like, that's why my reaction
25 to the nature of the objection, right, which I thought

DIRECT EXAMINATION - JONATHAN EMENS

1 didn't really make sense. It's like you can go spend time
2 and have the guy testify about the substance of this, but
3 it's not prior art.

4 MR. MILLIKEN: And if I may, Your Honor, the
5 sort of -- the nature of having to print material off a
6 website means that, you know, the thing that ends up on the
7 page, it's going to have, you know, the date that the
8 website was accessed, it's never going to be an absolutely
9 perfect representation of what was on the --

10 THE COURT: Well, you say that, and this is
11 actually where I don't know enough to know whether that's
12 true or not. Because the way you described Wayback and the
13 hyperlinks suggested to me that, no, the hyperlink is, it's
14 going to tell you what the page looked like way back when.
15 That's the way I interpret it.

16 And I've got to tell you, but for the 2015
17 article, I don't know that this would even be an issue. But
18 it raises, in my mind, a concern about, well, what was
19 really on the website.

20 MR. MILLIKEN: Your Honor, on that point, I
21 think that it is -- it has to be clear that this wasn't
22 something from 2015 because, as I pointed out, if you go
23 above, it says, The study is not yet recruiting, which means
24 the study hadn't started. And the study was done in 2013.
25 That's how Vanda got FDA approval.

DIRECT EXAMINATION - JONATHAN EMENS

1 And so it cannot be the case that the contents
2 of this protocol is what some -- was what the protocol
3 looked like post-2015 because the study was over then and
4 the results were already available.

5 THE COURT: Where is this in the pretrial report
6 spotted as an issue?

7 MR. STONE: Your Honor, I believe the document
8 is called Statement of Additional Matters, but give us one
9 moment to grab a copy of it.

10 MR. MILLIKEN: I believe the Statement of
11 Additional Matters, I think that's specific to the Wayback
12 declaration issue, not the kind of broader issue of the
13 public admissibility of the clinicaltrials.gov --

14 THE COURT: Well, let's start here.

15 MR. STONE: Your Honor, that's because we
16 thought that's what the debate was.

17 THE COURT: Okay. Where is it?

18 MR. STONE: A colleague is going to bring a copy
19 of it.

20 It's Exhibit 15, Your Honor, to the pretrial
21 order in Paragraph 2. And some context may be helpful -- I
22 can see the Court is reading. I'll wait.

23 THE COURT: All right, Mr. Stone, I have read
24 it. Let me just ask you this, though.

25 What -- you say the deadline for close of fact

DIRECT EXAMINATION - JONATHAN EMENS

1 discovery is July 30, 2021, yet defendants did not disclose
2 until today the date the pretrial order was due to Court --

3 MR. STONE: Last month.

4 THE COURT: -- that they had this declaration.

5 Now, under what RFP or what -- what was it that
6 required them to disclose this declaration for the public
7 nature or any fact to establish the public nature of the
8 clinical trial's posting? Why were they required to
9 disclose that?

10 MR. STONE: In response to their invalidity
11 contentions, we had disclosed that we don't think this is
12 prior art.

13 THE COURT: Right.

14 MR. STONE: Then one of our experts opined that
15 it may not be prior art.

16 Frankly, in response to that expert report, had
17 they gone and gotten a declaration, I don't think we would
18 have said it was untimely. We went all the way through this
19 case having said we don't think that's prior art and they're
20 having said, essentially, what they said today, it says
21 July 15, 2010, and now we are saying, and it also says 2015.
22 At which time we -- on the day of the pretrial order, they
23 said, we're going to have a declaration to clear this up,
24 and I remember, with apologies, writing that paragraph
25 rather hurriedly on the date the pre-trial order was due.

DIRECT EXAMINATION - JONATHAN EMENS

1 Well, we just found out they had the
2 declaration -- their exhibit list said "declaration." But
3 that was all it said.

4 THE COURT: Right.

5 MR. STONE: I don't know who that is.

6 Then what happened is they produced a
7 declaration from the Wayback Machine which says -- and, you
8 know, the Wayback Machine could have come back and said,
9 this is a snapshot of the website as it existed July 15,
10 2010, and I don't think we would be standing here. Instead,
11 it came back and said, this is a snapshot of what existed on
12 the website in early 2011, which is too late for them --

13 THE COURT: Right.

14 MR. STONE: -- which is why they are not
15 offering the declaration because it doesn't help them.

16 And so where we are right now is we've told them
17 forever that you haven't proven up that this is prior art.
18 They, at the last minute, decided they would get a
19 declarant. It apparently did not work out for them very
20 well because it didn't prove it was prior art, and here we
21 are.

22 I take the Court's point that our objection
23 could easily have been that has no business being in the
24 courtroom. Part of the other issue is that they are
25 technically offering that word on that document -- I mean, I

DIRECT EXAMINATION - JONATHAN EMENS

1 guess it is three words -- to prove the truth of the matter
2 asserted. It's a hearsay objection.

3 To Your Honor's point, it is also a government
4 website. If it were integral, it had nothing unusual about
5 it, I would not be standing up in front of the Court and
6 saying, how do we know that's true. But there is reason to
7 believe that it isn't, namely it has something impossible on
8 it, and we've put this to them for years.

9 THE COURT: Okay. Mr. Milliken?

10 First of all, do you agree -- or I should say do
11 you dispute that in June of 2021 Vanda filed -- or served on
12 you objections and responses to the defendant's first set of
13 interrogatories regarding the '510, '511, '465, and '744
14 patents, and stated, quote: Furthermore, defendants have
15 not established the public nature of the alleged clinical
16 trials reference or that the information disclosed in
17 defendant's alleged reference was actually contained in
18 whatever was originally posted to clinicaltrials.gov,
19 unquote?

20 MR. MILLIKEN: I don't disagree with that. They
21 also disputed the public availability of a lot of our other
22 prior art.

23 THE COURT: I mean, what am I going to do,
24 right? I've got this issue before me, they've disputed it.

25 MR. MILLIKEN: Understood.

DIRECT EXAMINATION - JONATHAN EMENS

1 Your Honor, if I -- on the Wayback point, the
2 Wayback declaration captures the protocol as it existed in
3 March 2011, which is also before the priority date of the
4 patent.

5 THE COURT: Actually, hold on. Maybe you should
6 just give me the declaration. Is that --

7 MR. GROOMBRIDGE: We'd be happy to, Your Honor.

8 MR. MILLIKEN: The Wayback declaration, Your
9 Honor?

10 THE COURT: Sure.

11 MR. MILLIKEN: I would point out that this
12 version which actually captured the web page in March of
13 2011 does not have the 2015 article, and so it doesn't
14 present the same.

15 THE COURT: All right. So I'll read the
16 declaration, which, for the record, is marked DTX-410.1.
17 And it's got an exhibit attached to it, but I don't have the
18 cover sheet. Yes, I do. Sorry, now I see it.

19 Well, all right. I guess I'm a little confused.
20 So there's an explanation in this affidavit which was given
21 by apparently Nathaniel Frank-White. And he says in
22 paragraph six of the declaration: Attached hereto as
23 exhibit A are true and accurate copies of screenshots of the
24 Internet archive's records of the achieved files for the
25 URLs and the dates specified in the attached cover sheet of

DIRECT EXAMINATION - JONATHAN EMENS

1 each print out.

2 So then I've got what appears to be the printout
3 of a website, but I don't see the cover sheet telling me the
4 dates.

5 Can somebody explain this to me?

6 MR. GROOMBRIDGE: Yes, Your Honor.

7 THE COURT: In fairness, let's have Mr. Milliken
8 explain it to me since he's the proponent of it.

9 MR. GROOMBRIDGE: Certainly, Your Honor.

10 THE COURT: Mr. Milliken, as I'm looking at it,
11 what it says on the front page of the website, and it
12 appears to be a screenshot of the clinicaltrials.gov
13 website. So I don't have a cover sheet, but it says it was
14 last updated February 23rd, 2011.

15 MR. MILLIKEN: Correct, Your Honor. So that
16 would have been the most recent -- you know, the updates
17 happen every few months.

18 THE COURT: Right.

19 MR. MILLIKEN: That would have been as of when
20 that was captured which I believe was March 2011.

21 THE COURT: Oh, now I see it. On the upper
22 right-hand it says March 7, 2011, so that was when it was
23 supposedly captured, correct?

24 MR. MILLIKEN: Correct, according to the
25 Wayback --

DIRECT EXAMINATION - JONATHAN EMENS

1 THE COURT: Now, is March 7, 2011, before the
2 priority date?

3 MR. MILLIKEN: It is, Your Honor.

4 THE COURT: So, okay.

5 MR. GROOMBRIDGE: So, Your Honor, it's before
6 the priority date but it's less than a year before the
7 priority date, which means it can't be 102(b) prior art.
8 And before -- in the recent weeks we had an elaborate meet
9 and confer about -- when we saw this, we said this is not
10 early enough to be 102(b) prior art, are you now arguing
11 that it's now 102(a) prior art? Which could be -- if it's
12 less than a year prior -- things that are less than year
13 prior can under certain circumstances qualify as 102(a) art.

14 And we went back and forth about that because we
15 said that would change the proofs that were being presented.
16 102(a) prior art is has the ability to swear behind and
17 prove an earlier date --

18 THE COURT: I'm sorry. I always get -- I know
19 you patent lawyers know swear behind; what does that mean
20 again?

21 MR. GROOMBRIDGE: I'm sorry, Your Honor. So
22 there's a couple of things about Section 102(a) that are
23 different from 102(b). If something is 102(b) prior art,
24 it's prior art for all time. You can't remove it.

25 But if it's 102(a) prior art, you can prove the

DIRECT EXAMINATION - JONATHAN EMENS

1 inventors had it before that date. And the other thing
2 about 102(a) is it has to be work in the words of the
3 statute by another. And this isn't by another because it's
4 Vanda's own work.

5 And so we said we don't think this qualifies as
6 102(a) prior art and we had an elaborate meet-and-confer.
7 And, eventually, they said we're not relying on it for that.
8 We're relying on it for 102(b).

9 THE COURT: Okay. Mr. Milliken, are you relying
10 on this for 102(b) purposes?

11 MR. MILLIKEN: We're relying on the 2010 version
12 as 102(b) prior art. That's the version that Dr. Emens
13 relied on in his expert reports.

14 THE COURT: So that's not this version? When I
15 say "this," for the record, that's not the
16 clinicaltrials.gov's screenshot that was attached to the
17 affidavit of Nathaniel Frank-White?

18 MR. MILLIKEN: That was the March 2011 -- as it
19 existed, March 2011, which was the February 2011 version.

20 THE COURT: Okay.

21 MR. MILLIKEN: That's not the version Dr. Emens
22 relied on.

23 THE COURT: Oh, I got that, but you handed me up
24 this Vanda thing thinking it would help. Well, maybe I
25 asked for it. I don't know.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: But, Your Honor, I would point
2 out that under 102(a), Mr. Groombridge is quoting the used
3 by other -- or, you know, by another portion of the statute.
4 It also says: Or patented or described in a printed
5 publication before the invention thereof.

6 And, so, our point -- I think that even under
7 102(a), that document that you have in your hand that's
8 appended to the Wayback declaration, that would qualify as
9 102(a) prior art --

10 THE COURT: Right. But he's just said you guys
11 are not proffering it as 102(a), you're only proffering it
12 as under 102(b).

13 MR. MILLIKEN: The declaration corroborates that
14 the contents of the protocol, just the steps that Vanda was
15 doing as part of this protocol, that declaration
16 corroborates that that information was, in fact, available
17 before the priority date.

18 THE COURT: Yes.

19 MR. MILLIKEN: That was the purpose of the
20 Wayback declaration, to show that these --

21 THE COURT: But you're not trying to get in this
22 screenshot. That's part of the Wayback declaration.

23 MR. MILLIKEN: Agreed. But Your Honor can rely
24 on documents that are not in evidence in concluding that the
25 contents of the protocol are as they're reflected in

DIRECT EXAMINATION - JONATHAN EMENS

1 DTX-419. And I would also point out --

2 THE COURT: Hold on. Let's go step by step
3 before you get to the "also."

4 Okay. The exhibit attached to the Frank-White
5 affidavit reflects a screenshot taken March 7th of 2011 from
6 the clinicaltrials.gov website. The screenshot itself says
7 that the website had last been updated on February 23, 2011.

8 So I do think that the screenshot is probative
9 of what the website looked like as of February 23, 2011.
10 And, in fact, frankly, I'd be willing to accept it unless
11 somebody wants to impeach the Wayback declarant, okay. So
12 that gets me there.

13 Now, I don't understand how this declaration or
14 screenshot tells me or gives me confidence about what the
15 clinicaltrials.gov website looked like before February 23,
16 2011. So you said it does, so tell me how.

17 MR. MILLIKEN: I think I can explain that, Your
18 Honor.

19 So as I was describing earlier,
20 clinicaltrials.gov has this thing called history of changes
21 and it's essentially a list of hyperlinks that is the list
22 of the various versions of the protocol as they were posted.
23 And so the idea is, say I've got one that's July 2010 and
24 then the next is September 2010. I can click on the
25 July 2010 hyperlink and it will tell me what the protocol on

DIRECT EXAMINATION - JONATHAN EMENS

1 the website looked like --

2 THE COURT: As of the hyperlink date?

3 MR. MILLIKEN: -- until it was next updated in
4 September 2010.

5 THE COURT: Okay.

6 MR. MILLIKEN: And the reason the Wayback
7 declaration corroborates what I just said is if you look
8 at -- what's appended to the Wayback Machine and then
9 compare it to what you get, if you click on the
10 February 2011 update in the history of changes, it's going
11 to be the same.

12 THE COURT: Okay. All right. So then I think
13 we're back to kind of where I started, which is, so if you
14 have a witness come in and explain, I pulled whatever
15 document they want to say from the hyperlink on the
16 clinicaltrials.gov and this is what I get, I mean, at that
17 point is there even an objection to it coming in?

18 MR. GROOMBRIDGE: I think there would be, Your
19 Honor.

20 THE COURT: Okay.

21 MR. GROOMBRIDGE: Because I think what
22 Mr. Milliken is saying is that if you look at the
23 February 23rd -- or February 23rd, 2011, version on the
24 website, what you see is something that looks like this,
25 like what's appended to the screenshot. We don't dispute

DIRECT EXAMINATION - JONATHAN EMENS

1 that, right. That's fine.

2 Our problem is that the version that they want
3 to rely on plainly represents a mixture of information that
4 was available in 2010 and information that was not available
5 in 2010.

6 THE COURT: Right.

7 MR. GROOMBRIDGE: And they have never -- as
8 Mr. Stone said, for years we have told them that this was an
9 issue and they have never attempted to separate out those
10 things and to prove up what was there.

11 And now, you know, here we are in trial and, you
12 know, the music has stopped.

13 THE COURT: All right.

14 MR. MILLIKEN: Your Honor, can I make one
15 additional point?

16 THE COURT: Yes.

17 MR. MILLIKEN: So, in addition to the Wayback
18 declaration --

19 THE COURT: I don't know how the Wayback
20 declaration helps you at all.

21 MR. MILLIKEN: Okay.

22 THE COURT: So maybe if you want -- if you're
23 telling me it does help you, tell me how, because I don't
24 see it.

25 MR. MILLIKEN: Well, let me try this. There is

DIRECT EXAMINATION - JONATHAN EMENS

1 another document on the exhibit list that is an e-mail from
2 one of the named inventors in which Vanda employees are
3 saying are -- and this is from August 2010. Vanda employees
4 are saying: Our clinicaltrials.gov posting has been updated
5 to reflect that we are recruiting. And it attaches a
6 receipt from Vanda's submission to the clinicaltrials.gov
7 website.

8 And so, that clearly shows that Vanda did, in
9 fact, submit this protocol in --

10 THE COURT: What protocol?

11 MR. MILLIKEN: The Hetlioz Phase 3 trial
12 protocol.

13 THE COURT: What version of it?

14 MR. MILLIKEN: The first version.

15 THE COURT: All right. I'm just going to -- at
16 this point, I'm just going to step back and I'm going to
17 just apply the rules of evidence. And you can adduce
18 whatever you think you need to adduce to authenticate
19 whatever document you want to get in and I'll rule on the
20 admissibility of it when it's teed up for me.

21 I don't know the whole history, the
22 back-and-forth with the parties. I do know that as of
23 June 2021, your side was put on notice that there were
24 issues as to the authenticity of any document that you would
25 want to put in.

DIRECT EXAMINATION - JONATHAN EMENS

1 And so it's incumbent upon you to satisfy the
2 rules of evidence to get them into evidence. I don't know
3 whether you're going to be able to lay the necessary
4 foundation to accomplish that or not.

5 It may be that because of the back-and-forth
6 between the parties, you mentioned some longer exhibit, I
7 think Exhibit 42 or something, it may be that you want --
8 that there was at least misunderstanding or something said
9 that caused you to reasonably believe that you were going to
10 be able to get DDX-419 in as evidence of prior art.

11 And so if you want to have time to gather
12 yourself and figure out how you're going to get it
13 introduced, I'm willing to give you that time.

14 And I can't stress enough that Vanda -- its
15 objection, the way it articulated it at the beginning, was
16 unfortunate. Because the real issue ultimately goes to
17 establishing that the purported screenshot was the
18 screenshot as of July 15, 2010. That is the issue.

19 And I would have had to resolve it whether they
20 articulated it today as an authentication objection or a
21 relevance objection. Because my recollection is what
22 Mr. Groombridge said was, well, just want to note for the
23 record, the witness can testify about the substance of this,
24 but not lay -- but not testify that this substance was on
25 the website as of a certain date. Which I take is really an

DIRECT EXAMINATION - JONATHAN EMENS

1 authentication objection.

2 And however way you construe it, the issue I
3 think is very clear why it needs to be resolved. And I'm
4 going to resolve it now. I'm not going to wait until
5 post-trial briefing to resolve it.

6 MR. MILLIKEN: At the risk of repeating myself,
7 Vanda's counsel explicitly represented to me that there was
8 no evidentiary objection. But I understand.

9 THE COURT: And that's why I kind of -- I feel
10 for you. You know what I mean? But we got to resolve it
11 now. We're not going to be able to resolve it in post-trial
12 briefing, right.

13 And I'm not going to -- I don't want to sit here
14 for another couple of hours listening to this -- all this
15 testimony about this website when it turns out we don't
16 really know whether this website looked like it did in
17 July of 2010.

18 MR. MILLIKEN: If I could, Your Honor, clarify
19 the role that this document plays in our invalidity case,
20 just in case it's helpful.

21 So on the RE604 patent, we have two obviousness
22 combinations. Neither one of them uses this document. The
23 reason that we use this document as a conditional argument
24 for anticipation, our point is that the -- let me try to
25 explain. I'm sorry.

DIRECT EXAMINATION - JONATHAN EMENS

1 So the clinical trial protocol for the Hetlioz
2 Phase 3 trial discloses administering 20 milligrams of
3 tasimelteon an hour before bedtime to blind Non-24 patients.
4 That's what they were studying. That is also what our
5 labels say. It says: Administer 20 milligrams tasimelteon
6 an hour before bedtime to blind Non-24 patients.

7 They are taking the position that that label
8 necessarily induces infringement of the claimed method.

9 So, in other words, if you do those four things,
10 20 milligrams tasimelteon an hour before bedtime to blind
11 Non-24 patients, you're going to get the entraining and
12 maintaining limitations. And our point is, if that is
13 correct, then this protocol that was publically available in
14 July 2010 which discloses those same mechanical steps,
15 that's got to anticipate. Because as Mr. Rozendaal --

16 THE COURT: Are those the only limitations of
17 the claim?

18 MR. MILLIKEN: So it's the four that I mentioned
19 plus entraining the patient to the 24-hour and maintaining
20 that --

21 THE COURT: Right.

22 MR. MILLIKEN: And it's an example, as
23 Mr. Rozendaal said in his opening of the principle that that
24 which infringes, if it comes after the patent, anticipates
25 if it comes before the patent. And that's the reason the

DIRECT EXAMINATION - JONATHAN EMENS

1 document is in the case.

2 MR. GROOMBRIDGE: And, Your Honor --

3 THE COURT: Just give me a second, please.

4 MR. MILLIKEN: Are you looking for the patent,
5 Your Honor?

6 THE COURT: Yes.

7 MR. MILLIKEN: It's JTX-1. It should be at the
8 front of the binder.

9 THE COURT: Okay. So I appreciate the
10 importance of it. It's pretty important.

11 MR. MILLIKEN: We believe it's important.

12 THE COURT: I could see why.

13 MR. GROOMBRIDGE: Your Honor, I just wanted to
14 note that we do not agree with the argument -- that the
15 argument is correct. It's something that the parties
16 dispute as to what would be the legal consequences if this
17 is what -- at the time of this study, nobody knew whether it
18 entrained and, so --

19 THE COURT: Nobody knew what?

20 MR. GROOMBRIDGE: Nobody knew whether
21 tasimelteon would entrain. That was the purpose of the
22 study. And so, the argument that it discloses entrainment,
23 we disagree with.

24 THE COURT: Okay.

25 (Discussion held off the record.)

DIRECT EXAMINATION - JONATHAN EMENS

1 THE COURT: All right. So Mr. Milliken, so it
2 is very important, I get it. And I think you should do your
3 best to lay whatever foundation you need to lay to establish
4 that whatever screenshot you want to put in front of me was,
5 in fact, posted on the clinicaltrials.gov website as of the
6 day that the witness says the screenshot was posted. Okay.
7 That's incumbent upon you, it seems to me, and that's where
8 we are.

9 Do you want -- is that something you need time
10 to put together?

11 MR. MILLIKEN: If Your Honor wouldn't mind.

12 THE COURT: I'm happy to do it, because I think
13 it's very important. And I don't have the wherewithal or
14 knowledge to arbitrate the back-and-forth.

15 But in fairness to Vanda, I will say this, I
16 mean, this was definitely a live issue. It was a live issue
17 as of the submission of the pretrial report. I vaguely --
18 was there some mention of it at the pretrial conference? My
19 recollection is there was mention of it and then we'll go
20 and try to resolve it, something like that.

21 MR. STONE: Your Honor, you're exactly right.
22 The reason for that is that in the pretrial order we wrote
23 about a declaration --

24 THE COURT: You didn't have it.

25 MR. STONE: Correct. I stood at this lectern

DIRECT EXAMINATION - JONATHAN EMENS

1 because we saw the screenshot attached to it as not helping
2 them. It's within the one-year period for 102(b). What we
3 said was we don't need to depose the declarant from the
4 Wayback Machine. We're not disputing that that is, in fact,
5 true.

6 THE COURT: Right.

7 MR. STONE: And so what I had said was there
8 wasn't going to be a fight about the declaration itself.
9 And, in fact, as Your Honor has pointed out several times
10 today, there isn't. That is a true and correct copy of
11 whatever the Wayback Machine had in March of 2011. We don't
12 dispute that.

13 THE COURT: Okay.

14 MR. STONE: But we didn't waive the objection
15 that they haven't proven what was available in July of 2010,
16 Your Honor is exactly right that that's the issue.

17 THE COURT: All right.

18 Mr. Milliken, what do you need?

19 MR. MILLIKEN: Just one moment, Your Honor.
20 Would 15 minutes be all right?

21 THE COURT: Yes, that's fine. Okay. We'll
22 break for 15 minutes. We'll come back at 11:15.

23 (Recess taken.)

24 THE COURT: Have a seat.

25 Mr. Milliken.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: Thank you, Your Honor. This was
2 the version that was disclosed to the plaintiffs and there
3 was an objection, but I'd like to lay a foundation for it.

4 THE COURT: This is an exhibit that -- have I
5 seen it before?

6 MR. MILLIKEN: No, I'm about to hand a copy up
7 to Your Honor.

8 THE COURT: Okay.

9 MR. MILLIKEN: May I approach to put one at the
10 witness stand?

11 THE COURT: Go ahead, yes.

12 MR. MILLIKEN: Thank you.

13 THE COURT: All right. So there's an objection
14 to this exhibit?

15 MR. GROOMBRIDGE: Your Honor, we don't object if
16 Mr. Milliken wants to attempt to lay a foundation for this.

17 THE COURT: Okay.

18 MR. MILLIKEN: So I think we're ready for
19 Dr. Emens.

20 THE COURT: All right. Bring him back in.

21 (Whereupon, Dr. Emens retook the stand and
22 testified as follows:)

23 THE COURT: All right. You remain under oath.
24 Have a seat.

25 THE WITNESS: Thank you.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: May I proceed, Your Honor?

2 THE COURT: Yes, please.

3 BY MR. MILLIKEN:

4 Q. Dr. Emens, do you see laid on top of your binder on
5 the witness stand is a document that says DTX-42 at the
6 bottom right-hand corner?

7 A. I do.

8 Q. Do you recognize this document?

9 A. I do.

10 Q. Is this a compilation of updates from the clinical to
11 the Hetlioz clinical trial protocol from the
12 clinicaltrials.gov website?

13 A. Yes, it is.

14 Q. Okay. I'd like you to -- so, first of all, on the
15 cover of the document, could you read the title of this
16 study, please?

17 A. Yeah, it's: Efficacy and Safety of Tasimelteon
18 Compared With Placebo in Totally Blind Subjects With
19 Non-24-Hour Sleep-Wake Disorder.

20 Q. Could you flip over to page 7.

21 A. Yes.

22 Q. Do you see about, I don't know, halfway down the page
23 there it says: Publications automatically indexed to this
24 study by clinicaltrials.gov identifier, and it says NCT
25 number?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yes.

2 Q. And then do you see that there's a citation to -- it
3 looks like a publication?

4 A. Yes, I do.

5 Q. And what publication is that?

6 A. So this is the result of the set and reset trials
7 that was published in The Lancet in 2015.

8 Q. Okay.

9 A. The results of the Phase 3 trial.

10 Q. Okay. Could you now turn to DTX-49.2.

11 A. Is that in my binder?

12 Q. No, sorry. It's the document you were just looking
13 at. It's just page 9.

14 A. Okay.

15 Q. 42.9. I'm sorry. I misspoke.

16 A. Okay. That's why I was confused. Okay. Yes, I'm
17 there.

18 Q. Do you see it says study NCT, and then there's a
19 bunch of numbers?

20 A. Yes, I do.

21 Q. And then what is the date listed on this study?

22 A. July 13th of 2010.

23 Q. And then if you go down a little bit, do you see an
24 entry that says "first submitted"?

25 A. I do.

DIRECT EXAMINATION - JONATHAN EMENS

1 Q. What's the date listed there?

2 A. July 2nd of 2010.

3 Q. And then below that it says: First submitted that
4 met QC criteria.

5 A. Yeah, July 13th, 2010.

6 Q. And then below that it says "first posting"?

7 A. Yes, July 15th of 2010.

8 Q. Okay. Could you go now to DTX-42.11.

9 A. Yes, I'm there.

10 Q. And take a look at the bottom of that page.

11 A. Yes.

12 Q. And you see there's a citation to a Lockley article?

13 A. Yes.

14 Q. Is this the Lockley article that was automatically
15 indexed to the clinical trial protocol?

16 A. Yes, it is. It's the same Lancet 2015 article.

17 Q. All right. Could we now go to DTX-42.13.

18 A. Yes.

19 Q. You see, again, it has the study number and it says
20 "on date" below that about a third of the way down the page?

21 A. Yes.

22 Q. What's the date there?

23 A. August 26th of 2010.

24 Q. And then if you look down about two-thirds of the
25 way, there's a line that says: Last update posted.

DIRECT EXAMINATION - JONATHAN EMENS

1 Do you see that?

2 A. Yes.

3 Q. What's that date?

4 A. August 27th of 2010.

5 Q. And then if you move to DTX-42.16.

6 A. Yes.

7 Q. Do you see a reference to a Lockley 2015 article?

8 A. I do.

9 Q. And is this the Lockley 2015 article that was
10 automatically indexed to this study --

11 A. It was -- is.

12 MR. GROOMBRIDGE: Your Honor, we object in
13 this -- this doesn't seem like it's foundation, and there's
14 nothing about automatic indexing in his expert report. He's
15 obviously just used the words, but --

16 THE COURT: I know you already let one in, you
17 know that.

18 MR. GROOMBRIDGE: Yes, I did.

19 But none of this is in -- to the extent he's
20 just going through reading the documents, that's fine. But
21 the -- there's nothing in the expert report about how the
22 website works, which is where this seems to be going.

23 THE COURT: Okay. So the objection is what?
24 Foundation or --

25 MR. GROOMBRIDGE: Foundation and untimely

DIRECT EXAMINATION - JONATHAN EMENS

1 disclosure.

2 THE COURT: I guess it's sustained. I don't
3 guess. It is sustained.

4 BY MR. MILLIKEN:

5 Q. All right. Could you go back, Dr. Emens, to
6 DTX-42.9.

7 A. Yes, I'm there.

8 Q. And I believe that you testified that this is the
9 first version of the protocol that was posted in July 2010;
10 is that right?

11 A. Yes.

12 MR. GROOMBRIDGE: Objection, Your Honor. Again,
13 foundation that this witness has no basis to testify whether
14 this was or wasn't posted.

15 THE COURT: Well, the question actually asked:
16 I believe you testified that this is the first version. I
17 don't know if he did or not.

18 So, I think he actually has a basis to testify
19 about what he testified about, right? That's actually the
20 question that's pending.

21 So that objection is overruled.

22 BY MR. MILLIKEN:

23 Q. Dr. Emens, have you visited clinicaltrials.gov
24 recently?

25 A. I have.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: With the Court's permission,
2 could we bring up clinicaltrials.gov on the screen?

3 THE COURT: You mean live?

4 MR. MILLIKEN: Yes.

5 THE COURT: Yes.

6 MR. MILLIKEN: Mr. Brooks, could we pull up a
7 web browser, please.

8 Could you type in www. -- oh, you're already
9 there.

10 BY MR. MILLIKEN:

11 Q. And, Dr. Emens, the condition that we're talking
12 about here is Non-24, right?

13 A. Mm-hmm.

14 MR. MILLIKEN: Could we search Non-24 in
15 condition or disease.

16 And click on Non-24-Hour Sleep-Wake Disorder and
17 click "search."

18 Then could we scroll down.

19 BY MR. MILLIKEN:

20 Q. Dr. Emens, do you see trial record number five?

21 A. I do.

22 Q. Is that the Hetlioz Phase 3 trial that we've been
23 discussing for the last little bit?

24 A. It is.

25 MR. MILLIKEN: Could we click on that hyperlink,

DIRECT EXAMINATION - JONATHAN EMENS

1 please, Mr. Brooks.

2 BY MR. MILLIKEN:

3 Q. When you visited clinicaltrials.gov recently,
4 Dr. Emens, did you click on the part that says: How to read
5 a study record?

6 A. I did.

7 MR. MILLIKEN: Could you click on that,
8 Mr. Brooks.

9 BY MR. MILLIKEN:

10 Q. And did you further click on the part that says:
11 Historical Views of Records?

12 A. I did indeed.

13 MR. MILLIKEN: Could we click on that, please,
14 Mr. Brooks.

15 BY MR. MILLIKEN:

16 Q. Could you read what it says under Historical Views of
17 Records?

18 MR. GROOMBRIDGE: Objection, Your Honor. Again,
19 this is --

20 THE COURT: When you say "again," this is the
21 first, so we're not on again.

22 Go ahead.

23 MR. GROOMBRIDGE: I'm sorry.

24 But this seems to be an attempt to go into the
25 workings of clinicaltrials.gov, none of which is in his

DIRECT EXAMINATION - JONATHAN EMENS

1 expert report. So we object to it as untimely disclosure
2 and prejudicial because we're seeing this now for the first
3 time in open court.

4 THE COURT: Well, first of all, is it your
5 position that he did not even use the words
6 "clinicaltrials.gov" in his expert report?

7 MR. GROOMBRIDGE: In his report, the sum total
8 of the disclosure is in Paragraph 84 where he said: I have
9 reviewed the summary of this clinical trial as published at
10 the public website clinicaltrials.org in July 2010 which is
11 available in the History of Changes section of the
12 clinicaltrials.gov website called NCT 01163032.

13 And that's what he says. He doesn't go into any
14 explanation of how it works or what these things mean or how
15 one may arrange or retrieve information or how the website
16 is maintained. None of that was addressed. It's simply
17 saying, I looked at the website.

18 And, you know, plainly, as Your Honor has seen
19 now repeatedly, this is -- has been a dispute at issue for
20 two years in the case, and we think it's untimely and
21 prejudicial to now be confronted with this at, you know, in
22 real time at trial.

23 MR. MILLIKEN: Your Honor, his expert report
24 clearly states that he relied on the History of Changes
25 feature of clinicaltrials.gov, and this goes to --

DIRECT EXAMINATION - JONATHAN EMENS

1 THE COURT: Can you show me that?

2 MR. MILLIKEN: I believe that I may have handed
3 my copy to Your Honor. It's in Paragraph 84 of his
4 1/31/2020 expert report.

5 THE COURT: The pending question is: Could you
6 read what it says under Historical Views of Records.

7 I'm going to overrule the objection, but let's
8 see -- I mean, just because of that specific question. I'm
9 going to go question by question and we'll see.

10 BY MR. MILLIKEN:

11 Q. You may answer the question, Dr. Emens.

12 A. Yeah, I'll read under Historical View of Records. It
13 says: You can access the historical view of each record by
14 clicking on the History of Changes link near the bottom of
15 the full text view of each record. Historical views show
16 you when a record is updated and how it was changed.

17 Q. Okay.

18 MR. MILLIKEN: Could we go back, Mr. Brooks, to
19 the previous tab -- sorry. It looked like it opened a new
20 tab. Yes, correct.

21 Could we now scroll all the way down towards the
22 bottom of the page.

23 BY MR. MILLIKEN:

24 Q. Do you see there, Dr. Emens, where it says History of
25 Changes?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yeah. Yes.

2 Q. When you visited clinicaltrials.gov recently, did you
3 click on History of Changes?

4 A. I did, indeed.

5 MR. MILLIKEN: Could you click on that,
6 Mr. Brooks.

7 And then if you could scroll up, please.

8 BY MR. MILLIKEN:

9 Q. When you visited History of Changes recently,
10 Dr. Emens, which version of the protocol did you click on?

11 A. So the earliest one, the one at the top. Submitted
12 date of July 13th of 2010.

13 Q. Okay.

14 MR. MILLIKEN: Could we click on that, please.

15 BY MR. MILLIKEN:

16 Q. And I'd like you, if you could, to look at DTX-49.2
17 that you have in front of you and see if you could compare
18 it to what we have on the screen that you got in the
19 July 2010 version in the History of Changes record.

20 MR. GROOMBRIDGE: Your Honor --

21 MR. MILLIKEN: For the record, it's 42.9. I
22 misspoke again.

23 MR. GROOMBRIDGE: I'd like to renew the
24 objection.

25 THE COURT: Well, when you say "renew," what's

DIRECT EXAMINATION - JONATHAN EMENS

1 the objection?

2 MR. GROOMBRIDGE: The objection is that this
3 is -- it's an untimely disclosure, not in his expert report,
4 and it's prejudicial given the circumstances here.

5 THE COURT: What's not in his expert report?

6 MR. GROOMBRIDGE: The sole disclosure in his
7 expert report is the statement that I read earlier, Your
8 Honor, saying that he's reviewed this, which is available in
9 the History of Changes section of the current
10 clinicaltrials.gov website. That's it. That's all he said.
11 He didn't get into any explanation of it or how it works or
12 what is the significance of different links within the
13 section of the website. Or, indeed, comparing different
14 versions, none of that is in here.

15 THE COURT: What are you referring to? Are you
16 referring to Paragraph 84 of your report?

17 MR. MILLIKEN: Are you asking me?

18 THE COURT: No, I'm asking Mr. Groombridge.

19 MR. GROOMBRIDGE: Yes, Your Honor, I'm referring
20 to Paragraph 84.

21 THE COURT: All right. Okay.

22 So here's -- for the record, Paragraph 84 reads
23 as follows: Phase 3 clinical trial that was disclosed
24 publically in July 2010 plan to administer 20 milligrams of
25 tasimelteon or placebo daily to Non-24 patients for a

DIRECT EXAMINATION - JONATHAN EMENS

1 six-month period. The patients were given tasimelteon or
2 placebo one hour prior to bedtime. The initial primary
3 outcome measure was subjective average total nighttime sleep
4 measured in weeks 3 to 6.

5 In other words, the study sponsors were looking
6 to see if tasimelteon was efficacious in the treatment of
7 Non-24 by assessing changes in total nighttime sleep in
8 Non-24 patients.

9 A secondary outcome measure was stabilization of
10 phase relationship between circadian melatonin rhythm and
11 the timing of sleep.

12 I reviewed the summary of this clinical trial as
13 published at the public website clinicaltrials.org in July
14 of 2010, which is available in the History of Changes
15 section at the current clinicaltrials.gov website for this
16 study called NCT 01163032.

17 Clinicaltrials.gov identifier: NCT 01163032,
18 and then the title in quotes, "Efficacy and Safety of
19 Tasimelteon Beyond Compared With Placebo in Totally Blind
20 Subjects With Non-24-Hour Sleep-Wake Disorder," July 15,
21 2010.

22 All right. So what this is doing is offering an
23 opinion about the content of the clinical trial as it
24 existed in July of 2010.

25 And so I think his testimony is admissible on

DIRECT EXAMINATION - JONATHAN EMENS

1 the subject matter of the clinical study as it existed as of
2 July 2010.

3 And now we are, as I understand it, trying to
4 get into evidence a document that -- or a website that
5 memorializes what the study looked like as of July 2010.

6 And its a factual question, that does not
7 necessarily require an expert opinion to adduce in court
8 what is an exhibit which accurately reflects what the
9 clinical trial data looked like as of July 2010.

10 I think that's the issue that we're grappling
11 with right now. I think it's fair game for the witness to
12 be asked questions to put into evidence that exhibit.

13 Before I decide its authenticity or whether I'd
14 admit it, I'll permit cross-examination. All right.

15 MR. MILLIKEN: Thank you, Your Honor.

16 BY MR. MILLIKEN:

17 Q. Dr. Emens, this version of the clinical trial
18 protocol that we're looking at on the screen, what date does
19 this say at the top?

20 A. Submitted date is July 13, 2010.

21 Q. And is this the version of the clinical trial
22 protocol that you relied on in your invalidity analysis in
23 this case?

24 A. It is.

25 Q. Okay. If you could now look down and compare what

DIRECT EXAMINATION - JONATHAN EMENS

1 you have in front of you DTX-42.9 to what's displayed here
2 on the screen.

3 And if you could take a look specifically at the
4 Brief Title, is the Brief Title the same in both documents?

5 A. It is.

6 MR. MILLIKEN: And if we scroll down just a bit.

7 BY MR. MILLIKEN:

8 Q. The first submitted date, is that the same?

9 A. It is. They're both July 2nd of 2010.

10 Q. And a little bit further down you see the last update
11 posted. Is that the same?

12 A. Yeah, they are both July 15th of 2010.

13 MR. MILLIKEN: And then if we could go down a
14 little bit more to where it says Brief Summary.

15 BY MR. MILLIKEN:

16 Q. Could you compare the text in the Brief Summary
17 section and let me know if that's the same?

18 A. They are the same.

19 Q. Take your time, but if you could also take a look at
20 the Detailed Description section that's on the screen and
21 compare it to what you have in the document in front of you
22 and let me know if that's the same.

23 A. They are the same.

24 MR. MILLIKEN: And then could we scroll down a
25 little bit more to the Arms and Interventions section.

DIRECT EXAMINATION - JONATHAN EMENS

1 BY MR. MILLIKEN:

2 Q. Could you compare the Arms and Interventions section
3 that's on the screen with the document you have in front of
4 you at DTX-42.10?

5 A. They are the same.

6 Q. All right.

7 MR. MILLIKEN: And then if you could scroll
8 down, Mr. Brooks, down to the very end.

9 BY MR. MILLIKEN:

10 Q. And do you see on the screen, Dr. Emens, underneath
11 References it says: Links and available IPD/Information,
12 but it's otherwise blank?

13 A. Yes.

14 Q. And then do you see on DTX-42.11, underneath
15 References, there's a citation to the Lockley 2015 article
16 that we were looking at earlier?

17 A. Yes, I do see that.

18 Q. Do you think that that citation to the 2015 Lockley
19 article was there in 2010 when this clinical trial protocol
20 was first posted on the website?

21 MR. GROOMBRIDGE: Objection, Your Honor, calls
22 for speculation.

23 THE COURT: Sustained.

24 BY MR. MILLIKEN:

25 Q. This Lockley 2015 article that is listed, that goes

CROSS-EXAMINATION - JONATHAN EMENS

1 from DTX-42.11 to DTX-42.12, is that the same Lockley
2 article that DTX-42.7 states is, quote: Automatically
3 indexed to the study by clinicaltrials.gov identifier NCT
4 number?

5 A. Yes, it's same Phase 3 outcome study that was
6 published in The Lancet in 2015.

7 MR. MILLIKEN: Your Honor, I offer DTX-42 into
8 evidence.

9 MR. GROOMBRIDGE: Your Honor, may we
10 cross-examine briefly?

11 THE COURT: Yes.

12 CROSS-EXAMINATION

13 BY MR. GROOMBRIDGE:

14 Q. Good morning, Dr. Emens.

15 A. Good morning.

16 Q. I guess good afternoon.

17 Do you have DTX-42.9 -- 42 in front of you,
18 DTX-42?

19 A. DTX-42.1?

20 Q. The first page is DTX-42.1. So the whole exhibit, I
21 think, is DTX-42.

22 A. Yes, I do.

23 Q. Could you turn to DTX-42.9, please?

24 A. Yes, I'm there.

25 Q. And when you were being asked foundational questions,

CROSS-EXAMINATION - JONATHAN EMENS

1 one of the things you were asked was, what was the date
2 first posted.

3 Do you remember that?

4 A. Yes.

5 Q. And you said July 15, 2010, correct?

6 A. Correct.

7 Q. After that it says "estimate." Correct?

8 A. Yes.

9 Q. And, in fact, several of the dates that you testified
10 about just now say "estimate" after them, do they not?

11 A. Yes.

12 Q. Now, is this document in front of us, DTX-42, the
13 document, and specifically 42.9 -- Pages 9 through 12, the
14 document on which you have based your opinions about the
15 so-called clinical trial reference throughout your work on
16 this case?

17 A. Yes.

18 Q. Thank you.

19 MR. GROOMBRIDGE: Nothing further for now, Your
20 Honor.

21 We would object to the admission of -- on the
22 basis --

23 (Discussion between counsel held off the
24 record.)

25 MR. GROOMBRIDGE: So, Your Honor, we object on

CROSS-EXAMINATION - JONATHAN EMENS

1 the basis of relevance in that the -- if it can't be shown
2 when it became publically available in the form that we're
3 looking at here, then it doesn't qualify as prior art. And
4 it is, therefore, not germane to the dispute.

5 THE COURT: All right.

6 MR. MILLIKEN: May I respond to that, Your
7 Honor?

8 THE COURT: Sure.

9 MR. MILLIKEN: Your Honor, what we're looking at
10 on the screen is a self-authenticating US government website
11 that states that this version of the protocol was posted on
12 July 15, 2010, 18 months before the priority date of the
13 patent. And what we -- what I have just done is laid a
14 foundation for the proposition that the contents of DTX-42,
15 going from Pages 9 to 12, the contents of the protocol
16 accurately reflects what is on the self-authenticating US
17 government website.

18 THE COURT: So basically what we have here is
19 the application of the transitive property. If this looks
20 like 42 and because he's read them and he compared the
21 substance and they're identical, therefore he can testify
22 and we can admit Exhibit 42. Right?

23 MR. MILLIKEN: That's correct, Your Honor.

24 THE COURT: And you want me to take judicial
25 notice of the website.

DIRECT EXAMINATION - JONATHAN EMENS

1 MR. MILLIKEN: Correct, Your Honor, and I think
2 that's supported by Third Circuit precedence, and I'm happy
3 to provide you a cite.

4 THE COURT: All right. I'm going to admit it on
5 that basis.

6 All right, go ahead.

7 DIRECT EXAMINATION

8 BY MR. MILLIKEN:

9 Q. Okay. Let's get back to tasimelteon, shall we.

10 So --

11 THE COURT: One of the more unusual evidentiary
12 questions I have ever had, that's for sure, and I don't know
13 if there's an appeal issue or not, but -- and I do think
14 this could have been made a lot easier. There could have
15 been steps -- and, of course, I wasn't involved in figuring
16 all this out pretrial, but you were on notice, in fairness
17 to Vanda, that this was an issue.

18 But I will also say, and the case law is very,
19 very clear, the burden imposed by 901 is not very high; and
20 that also is the reason why I'm going to exercise my
21 discretion and let this in.

22 MR. MILLIKEN: Thank you, Your Honor.

23 BY MR. MILLIKEN:

24 Q. So Dr. Emens, just to confirm before we move on, did
25 you rely on the July 2010 version of the Hetlioz Phase 3

DIRECT EXAMINATION - JONATHAN EMENS

1 trial protocol in forming your opinions?

2 A. Yes.

3 Q. What was the administration protocol for the
4 treatment arm of this study?

5 A. It was an administration of 20 milligrams of
6 tasimelteon by mouth over a six-month period of time.

7 Q. And when did the patients take the tasimelteon?

8 A. So, if you can look at that, they took the
9 melatonin -- the tasimelteon prior to bedtime.

10 Q. Okay. And I apologize if you said this already, but
11 what condition did these patients have?

12 A. They were blind individuals with Non-24.

13 Q. All right. Let's now go back to your binder, and if
14 you could turn, please, to DTX-20.

15 THE COURT: And, actually, while you're looking
16 at that, Doctor, I just want to also, just to make sure the
17 record is complete, I found particularly probative on my
18 decision to allow the exhibit to be introduced the automatic
19 referral language on the website, which, in my mind,
20 indicates that what happens is when you access the website
21 at times, the studies, i.e., the 2015 study, for example, is
22 automatically attached to the website when it's accessed.

23 And also on the cross-examination of the witness
24 prior to my decision to allow the exhibit to be introduced,
25 there was really nothing to cast doubt on the fact that all

DIRECT EXAMINATION - JONATHAN EMENS

1 the other substance in Exhibit 42 is consistent with what's
2 on the website as accessed by the historic link; that the
3 purpose of the link is precisely to allow people to be able
4 to access historical versions of these clinical trials; and
5 the website's maintained by United States government. All
6 right.

7 So now the record, I hope, is complete as to why
8 I allowed all this information. All right.

9 MR. MILLIKEN: Thank you, Your Honor.

10 BY MR. MILLIKEN:

11 Q. Dr. Emens, do you recognize DTX-20?

12 A. I do.

13 Q. What is this?

14 A. This is a review article by Lankford from 2011.

15 Q. And did you rely on Lankford in forming your
16 opinions?

17 A. I did.

18 MR. MILLIKEN: Your Honor, I move DTX-20 into
19 evidence.

20 MR. GROOMBRIDGE: No objection.

21 THE COURT: All right. It's admitted.

22 (DTX-20 admitted into evidence.)

23 BY MR. MILLIKEN:

24 Q. Dr. Emens, you mentioned that this was a review
25 article. What is Lankford reviewing?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. So Lankford is reviewing the use of tasimelteon to
2 treat insomnia.

3 Q. And does Lankford talk about the Rajarantnam studies
4 we were discussing this morning?

5 A. Yes, indeed it does. It summarizes both the Phase 2
6 and Phase 3 Rajarantnam studies that we talked about
7 earlier.

8 Q. And does Lankford say Non-24 specifically?

9 A. Yes. Specifically it notes that there is an ongoing,
10 as we have highlighted there on the left, Phase 3 trial of
11 tasimelteon in blind people of Non-24 assessing how
12 effective tasimelteon in a dose of 20 milligrams would be.

13 Q. And is that the Phase 3 trial described in the
14 clinical trials reference we were just looking at?

15 A. It is.

16 Q. Does Lankford say anything about tasimelteon's
17 potential in treating circadian rhythm sleep disorders?

18 A. Yeah. So as I've highlighted on the right, Lankford
19 talks about how tasimelteon has a high affinity for the MT-1
20 and MT-2 receptors that we've talked about in a way that's
21 similar to melatonin.

22 And as he next says: Tasimelteon should
23 therefore be especially well suited for the treatment of
24 circadian rhythm sleep disorders of which Non-24 is one.

25 Q. Okay. All right. Thank you, Dr. Emens.

DIRECT EXAMINATION - JONATHAN EMENS

1 And that takes us to the conclusion of our
2 tasimelteon timeline.

3 I'm going to skip through claim construction
4 because of a stipulations the parties reached to streamline
5 the proceedings, and I'd like to go straight to the asserted
6 claims.

7 Could you explain what's displayed here on
8 DDX-5.55?

9 A. Yes, these are the relevant patents of the case.

10 Q. All right. Let's start with Claim 3 of the RE604
11 patent.

12 Could you briefly summarize your opinions
13 regarding the validity of Claim 3?

14 A. Yeah. So Claim 3 of RE604 would be invalid as
15 obvious over the combination of the Lankford, Hack, and '244
16 Publication references, as well as obvious over the
17 Hardeland, Hack, and '244 Publication.

18 And it -- again, if the Court were to -- again,
19 this is what has been explained to -- by the lawyers to me,
20 but if the Court were to accept the infringement argument
21 that Vanda has stated, then it would also be anticipated by
22 clinical trials.

23 Q. All right. Let 's talk about obviousness first.

24 As it's -- as the legal standard has been
25 explained to you by the attorneys, what things do we need to

DIRECT EXAMINATION - JONATHAN EMENS

1 consider when we evaluate whether a claim is obvious?

2 A. So it was explained to me that I have to consider the
3 scope and the content of the prior art; what a person of
4 ordinary skill in the art, what their level of skill would
5 actually be; and then the differences, if any, between the
6 prior art and whatever is being claimed in the invention,
7 any secondary considerations for non-obviousness as well, if
8 there are any.

9 Q. And then if we're talking about a claim that's
10 allegedly obvious in light of more than one prior art
11 reference, is there anything else that we have to consider?

12 A. Yeah. I was asked to consider whether there would be
13 motivation to combine these references and whether I would
14 have a reasonable expectation of success if I did so.

15 Q. All right. Let's get into the claims in a little bit
16 more detail.

17 Now, in analyzing Claim 3 of the RE604, did you
18 also consider the limitations found in claims 1 and 2?

19 A. Yes.

20 Q. And it looks like you've done some color-coding of
21 the claim here on the slides. Could you explain what that
22 color-coding represents.

23 A. Yeah, so it's breaking up the different limitations
24 separately by color.

25 Q. And before we get into your obviousness opinions, I'd

DIRECT EXAMINATION - JONATHAN EMENS

1 like to ask you a question about this first limitation.

2 Do you see that phrase in the first limitation

3 "daily sleep period of approximately 7 to 9 hours"?

4 A. Yes.

5 Q. Could you explain in your opinion how a person of
6 skill in the art would interpret this phrase.

7 A. Yeah. So this has been talked about. And I think a
8 person of skill in the art would assume that this means a
9 person was mostly asleep. Again, has been referred to
10 earlier, they may briefly wake up, but that they would
11 awaken after a period of mostly sleep.

12 Q. And do you understand that Vanda's experts have
13 offered a different interpretation of this phrase?

14 A. I do.

15 Q. And what is that interpretation, as you understand
16 it?

17 A. That it would be a 7 to 9-hour period of sleepiness,
18 increased sleepiness.

19 Q. And why, in your view, is your interpretation the
20 plain and ordinary meaning of that phrase as it would be
21 understood by a person of skill in the art?

22 A. Because it's described as a period of sleep after
23 which you awaken and not a period of sleepiness after which
24 you arise and get out of bed.

25 So I think the commonsense meaning of that would

DIRECT EXAMINATION - JONATHAN EMENS

1 be that I'd actually slept for some portion of that time.
2 There's a common phrase used in sleep medicine, "sleep
3 opportunity." They could have used that phrase. That's
4 commonly used, but they didn't. It's a period of sleep. So
5 I think the commonsense interpretation would be that they
6 slept.

7 Q. Thank you, Dr. Emens.

8 I'd now like to talk about how the prior art
9 combinations that you summarized for us earlier apply to
10 Claim 3 of the '604 patent.

11 Let's begin with Lankford, Hack and the '244
12 Publication.

13 Does this combination of references teach or
14 suggest the first limitation of Claim 1?

15 A. It does. Both Lankford, Hack and the '244
16 Publication do so.

17 Q. All right. Let's begin with Lankford. What in
18 Lankford teaches or suggests the first limitation?

19 A. So Lankford clearly says that it's going to be used
20 for the treatment of blind individuals with Non-24-Hour
21 Sleep/Wake Disorder using the drug tasimelteon.

22 Q. And does Lankford contain any other disclosures that
23 would teach or suggest the concept of entrainment?

24 A. Yeah, it points out that tasimelteon has already been
25 proven to be a circadian phase-resetting drug. And, again,

DIRECT EXAMINATION - JONATHAN EMENS

1 as I talked about earlier, resetting phase, resetting the
2 time of the circadian pacemaker's mechanism by which you
3 achieve entrainment.

4 Q. And just for the record, the cull out of the slide
5 that you've been reading from here, is it DTX-20.6? Is that
6 right?

7 A. Yes.

8 Q. Let's move on to Hack now. What in Hack teaches or
9 suggests the first limitation of Claim 1 of the '604 patent?

10 A. So Hack clearly states that they were studying blind
11 individuals with free-running circadian rhythms. In other
12 words, they have the disorder Non-24. And that they were
13 attempting to entrain them to the sleep-wake cycles, it
14 says, highlighted at the end there.

15 Q. And were they successful in entraining them to a
16 24-hour sleep-wake cycle?

17 A. They were.

18 Q. And the cull out on the slide you have here is from
19 JTX-146 page 1; is that right?

20 A. Yes.

21 Q. Does Hack show whether the patients in its study
22 experienced a daily sleep period of approximately 7 to
23 9 hours?

24 A. They did. They showed that compared to the placebo,
25 those who were on melatonin got 6.6 hours of sleep, plus or

DIRECT EXAMINATION - JONATHAN EMENS

1 minus 1.1 hours, standard deviation. So that would
2 certainly be approximately 7 to 9 hours.

3 Q. And you culled out on the slide here Table 3 at Page
4 6 of JTX-146; is that correct?

5 A. Yes.

6 Q. Okay. Finally, what in the '244 Publication teaches
7 or suggests the first limitation of Claim 1?

8 A. So it discusses regulating circadian rhythms,
9 including the sleep-wake cycle, which, again, by regulating
10 circadian rhythms we would be resetting them. Which I would
11 take to mean the mechanism by which you achieve entrainment
12 for the treatment of a circadian rhythm disorder. Again, of
13 which Non-24 is.

14 Q. All right. Let's -- or, sorry. For the record, you
15 culled out portions of the '244 Publication from DTX-41.2
16 and 41.25; is that correct?

17 A. Yes.

18 Q. Let's now move on to the second limitation to
19 maintaining this 24-hour sleep-wake cycle.

20 Is this limitation found in your first
21 combination of references?

22 A. It is. It's found both in Hack and the '244
23 Publication.

24 Q. And where is it found in Hack?

25 A. So, Hack is clear that chronic usage of the drug is

DIRECT EXAMINATION - JONATHAN EMENS

1 necessary to remain entrained to the 24-hour day, so that's
2 clearly there.

3 Q. And you're reading here from JTX-146, Page 2?

4 A. Yes.

5 Q. And what about the '244 Publication? Where does that
6 teach or suggest maintaining the limitation?

7 A. So it states that to avoid relapse, that treatment
8 needs to continue for some time, which I would say is
9 synonymous with maintaining the treatment.

10 Q. And you're reading here from Pages 5 and 6 of DTX-41?

11 A. Yes.

12 Q. All right. Now, on to the third limitation, orally
13 administering 20 milligrams of tasimelteon.

14 Is this limitation found in your combination?

15 A. It is, both in the Lankford and the '244 Publication.

16 Q. Okay. Where is it in Lankford?

17 A. So as we have highlighted here, Lankford is, again,
18 disclosing that Phase 3 trial in blind individuals with
19 Non-24. And clearly points out that the trial is going to
20 be looking at 20 milligrams of tasimelteon.

21 Q. And you're reading here from DTX-20.6?

22 A. Yes.

23 Q. All right. How about the '244 Publication? Where
24 does that disclose the dosing limitation?

25 A. In two points that we've highlighted here, both

DIRECT EXAMINATION - JONATHAN EMENS

1 talking about administering MA-1, which is, again, is
2 tasimelteon in the dose range of 10 to 100 milligrams. But
3 then also it is specifically in the second highlighted area
4 administering a dose of 20 milligrams.

5 Q. And any reason why you'd pick 20 milligrams over the
6 other possible doses that are disclosed there?

7 A. Yeah. The idea is that you'd want the lowest
8 effective dose that's not going to give you side effects.
9 Or at least minimize side effects.

10 Q. And, for the record, you've culled out here the
11 claims of the '244 that are at DTX-41.25; is that right?

12 A. Correct.

13 Q. Now, let's look at the fourth and final of Claim 1.
14 And it looks here on the slide like you've highlighted both
15 that limitation and the additional limitation of Claim 3 in
16 green.

17 Could you explain why that is.

18 A. Yes. Because they are both addressing administration
19 relative to bedtime.

20 Q. Okay. Are these limitations found in your prior art
21 combination?

22 A. Yeah, both found in Lankford and if we go back in the
23 '244 publication.

24 Q. And where is the limitation regarding the timing of
25 the administration found in Lankford?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. So in Lankford, it's stated multiple -- points in
2 time that it's being administered 30 minutes prior to
3 bedtime in the three places that you can see highlighted on
4 the left.

5 Q. And is this discussing the tasimelteon insomnia
6 trials?

7 A. Yes.

8 Q. And you're reading here from DTX-20.5; is that right?

9 A. Correct.

10 Q. What about the '244 Publication? Where does that
11 disclose the timing of administration?

12 A. So, again, two locations here where it discusses
13 administering MA-1, again, which is tasimelteon, 30 minutes
14 for 0.5 hours prior to bedtime.

15 Q. And does it specify a dose there?

16 A. Yes, at the bottom it also specifies at the
17 20-milligram-per-day dosage.

18 Q. And it looks like on the slide you culled out
19 DTX-41.10, 25 and 26; is that right?

20 A. Yes, that is correct.

21 Q. All right. Finally, let's tackle Claim 2.

22 Does your combination of prior art disclose that
23 the patient receiving treatment is totally blind?

24 A. It does.

25 Q. And which references disclose this limitation?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Both Lankford and the Hack publication.

2 Q. Where does Lankford disclose this limitation?

3 A. So, again, in Lankford, we see the description of the
4 ongoing, at that point in time, Phrase 3 trial tasimelteon
5 in blind people with no light perception at two different
6 points in time, at two different points in the article.

7 Again, that's synonymous with totally blind individuals.

8 Q. And you're reading here from DTX-20.6; is that right?

9 A. Yes.

10 Q. And where does Hack disclose the totally blind
11 limitation?

12 A. So they clearly state that it is blind subjects who
13 are being studied as highlighted in purple on the left.

14 Q. And you called out a portion from Page 1 of JTX-146;
15 is that right?

16 A. I have.

17 Q. So to sum up, in your opinion, Dr. Emens, does the
18 combination of Lankford, Hack and the '244 collectively
19 disclose or suggest each limitation of the Claim 3 of the
20 RE604 patent?

21 A. It does.

22 Q. All right. I'd now like you to put yourself in the
23 mindset of a person of skill in the art before January 2012.

24 So would such a person have been motivated to
25 combine these three references to arrive at the invention

DIRECT EXAMINATION - JONATHAN EMENS

1 that's claimed in Claim 3?

2 A. Most definitely.

3 Q. And could you explain to the Court why that is.

4 A. Yes. So starting on the left, we have the Hack
5 publication that tells me that melatonin can entrain
6 individuals with Non-24. So I know melatonin can achieve
7 the desired treatment effect.

8 Then I have Lankford and the '244 Publication
9 telling me that I have a drug, tasimelteon, that's acting on
10 the same types of receptors, melatonin receptors. They
11 point out that it has the exact same mechanism and the
12 action; namely, it can reset the timing of the biological
13 clock. It can cause these phase shifts. And furthermore
14 that it can cause entrainment.

15 And, finally, that it would probably be an
16 effective treatment for, as they point out there, numerous
17 circadian rhythm sleep disorders, such as Non-24. So I
18 think they have a really clear motivation to want to combine
19 them.

20 Q. And so having combined these references -- I think
21 you touched on this a bit in your previous answer.

22 But having combined these references, would a
23 person of skill in the art have had a reasonable expectation
24 of success in arriving at the invention of Claim 3?

25 A. Yeah, definitely. I mean, Lankford kind of really

DIRECT EXAMINATION - JONATHAN EMENS

1 spells it out for us, as highlighted on the left. You know,
2 Lankford talks about how tasimelteon should be especially
3 well suited for the treatment of circadian rhythm disorders.
4 And, again, the '244 Publication similarly says it should be
5 effective in treating sleep disorders.

6 Q. Would Lankford's disclosure of the ongoing Phase 3
7 trial on tasimelteon in totally blind Non-24 patients have
8 had any impact on the person of skill in the art's
9 expectation of success?

10 A. Oh, yeah, clearly. I mean, if someone is going to be
11 spending the time and money to do a big Phase 3 trial, all
12 that effort, as well as money, then that would say to me,
13 and to a person of ordinary skill in the art, that clearly
14 there was a reasonable expectation that they are going to
15 succeed. Otherwise, I don't think they would have invested
16 the time and money in the Phase 3 trial.

17 Q. Thank you, Dr. Emens.

18 Let's now move to the second combination of
19 prior art that you mentioned. And that is Hardeland, Hack
20 and the '244. Since we've already gone through those last
21 two references, I'd like to focus just on Hardeland and what
22 it tells us.

23 A. Sure.

24 Q. So, first, does Hardeland teach or suggest the
25 entraining limitation of the '604 patent?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. It does.

2 Q. And where is that?

3 A. So you can see highlighted here it states that
4 tasimelteon is acting on melatonin receptor agonist and can
5 phase shift a circadian rhythm, which, again, as I have
6 pointed out, is the mechanism by which you would cause
7 entrainment. And he further kind of culls out the fact that
8 this would make it suitable for treating circadian rhythm
9 sleep disorders such as Non-24.

10 Q. And you've culled out a portion of the document on
11 the slide here that's DTX-16.1; is that right?

12 A. That's correct.

13 Q. All right. What about the 20-milligram dose? Does
14 Hardeland disclose this limitation?

15 A. Hardeland also discloses the 20-milligram dose, yes.

16 Q. And where is that?

17 A. Clearly stated, as we have highlighted here,
18 Hardeland states that: Effective doses of tasimelteon were
19 in that 20- to 50-milligram range. So that's clearly
20 disclosed.

21 Q. And you have a cull out here from page 7 of DTX-16;
22 is that right?

23 A. Yes.

24 Q. And, finally, as to the timing limitation, does
25 Hardeland disclose administering tasimelteon a half hour to

DIRECT EXAMINATION - JONATHAN EMENS

1 an hour and a half before a patient's targeted bedtime?

2 A. It does.

3 Q. And where does Hardeland disclose those limitations?

4 A. So Hardeland describes the trials looking at
5 administration of tasimelteon 30 minutes before bedtime is
6 highlighted on the left.

7 Q. And you have a cull out here from Page 6 of DTX-16;
8 is that right?

9 A. I do.

10 Q. So in summary, does the combination of Hardeland,
11 Hack and the '244 Publication collectively teach or suggest
12 each limitation of Claim 3 of the '604 patent?

13 A. They do.

14 Q. And would a person of ordinary skill in the art have
15 been motivated to combine these references to arrive at the
16 claimed invention?

17 A. Certainly.

18 Q. And why is that?

19 A. Similar to the reasons I already described, again,
20 just to reiterate a little bit, we know from Hack that
21 melatonin can entrain blind individuals with Non-24. '244
22 Publication and Hardeland tell me I have a drug,
23 tasimelteon, that binds in a way similar to melatonin, can
24 cause those same phase shifts as melatonin, and can be
25 useful for entrainment, which, again, is what Hack had shown

DIRECT EXAMINATION - JONATHAN EMENS

1 with melatonin.

2 And so, clearly, there would have been
3 motivation to combine these references.

4 Q. And the Hardeland reference, does that cite Vanda's
5 '244 patent publication?

6 A. Yeah, sorry. That's highlighted starting WO from
7 DTX-16.7. That's the '244 Publication. Exactly.

8 Q. And having combined these three references, would a
9 person of skill in the art have had a reasonable expectation
10 of success in arriving at the invention of --

11 A. Yes. Again, as I've stated before but now talking
12 about Hardeland, Hardeland points out quite explicitly that
13 tasimelteon should be useful for treating circadian rhythm
14 sleep disorders explicitly. As well as, and, again, this is
15 important, other types of entrainment difficulties.

16 So Hardeland calls out that it would be useful
17 for entrainment specifically. And what's interesting is
18 that Hardeland says you would expect this based on the fact
19 that it's a melatonin (inaudible), meaning it's a melatonin
20 agonist. So Hardeland is clearly not surprised here by
21 that.

22 And also on the left, Hardeland concludes that,
23 again, tasimelteon should be appropriate for phase shifting
24 the circadian clock and resetting the time after the 24-hour
25 biological clock. And, therefore, should be useful in the

DIRECT EXAMINATION - JONATHAN EMENS

1 treatment of circadian rhythm sleep disorders. And then as
2 I stated before, the '244 culls out that it should be
3 effective in treating sleep disorders.

4 Q. And these passages of Hardeland that you have been
5 discussing that you culled out on the slides, those are
6 DTX-16, pages 7 and 8; is that right?

7 A. Correct.

8 Q. That takes care of obviousness on the '604 patent.
9 So I will now move on to anticipation.

10 I think you briefly summarized your anticipation
11 position earlier.

12 So I'd just like to confirm, this clinical
13 trials reference, is that the Phase 3 trial protocol for
14 Hetlioz that we were looking at earlier?

15 A. Yes.

16 Q. And that is DTX-42, I believe.

17 A. Yes.

18 Q. All right. Based on what you understand from the
19 attorneys, what does it mean for a claim to be anticipated?

20 A. Yeah. So what was explained to me is that a claim
21 can be anticipated if every limitation in the claim can be
22 found in just a single example of the prior art. And, you
23 know, like I put it here at the bottom and what was
24 discussed earlier, again, what was explained to me is this
25 concept that if something that comes after the patent is

DIRECT EXAMINATION - JONATHAN EMENS

1 infringing, that same claim, if it came -- if it came prior
2 to the issuance of the patent would be anticipatory or
3 anticipate.

4 Q. Okay. Let's move to the claims. For a moment I'd
5 like to set aside the limitations in the preamble and just
6 look at the next one, which is treating a Non-24 patient by
7 administering 20 milligrams of tasimelteon.

8 Does the clinical trials reference disclose this
9 limitation?

10 A. Yeah, so the clinicaltrials.gov from 2010 that talks
11 about Non-24 Sleep-Wake Disorder highlighted in yellow to
12 correspond to what's in the RE604 Claim 1.

13 Q. And does it disclose the 20-milligram dose?

14 A. It does. So, again, highlighted in blue on the left
15 from clinicaltrials.gov from 2010 discloses 20 milligrams
16 tasimelteon, again, the same as the RE604 patent, again,
17 highlighted in blue on the right.

18 Q. And just for clarity for the record, you've been
19 looking at the title and the arms and interventions section
20 of the clinical trial protocol; is that right?

21 A. Yes.

22 Q. Now, moving on to the timing limitation, does
23 clinical trials disclose administering the tasimelteon half
24 an hour to an hour and a half before the targeted bedtime?

25 A. Yeah. So back in 2010, clinical trials highlighted

DIRECT EXAMINATION - JONATHAN EMENS

1 in green on the left clearly states that tasimelteon placebo
2 is going to be administered about an hour prior to bedtime.

3 Q. And are you reading there from the detailed
4 description section of the clinical trial protocol?

5 A. Yes.

6 Q. And, finally does the clinical trial protocol
7 disclose that the patients were totally blind?

8 A. Yes, it's in the title. So in clinicaltrials.gov, it
9 states in purple totally blind subjects, again, the same as
10 in Claim 2 of the RE604 patent.

11 Q. All right. I'd now like to go back to what we
12 skipped, the preamble of Claim 1.

13 Were you present in the courtroom on I believe
14 it was Monday when Dr. Combs testified?

15 A. I was.

16 Q. And did you hear him give the opinion that if you
17 give tasimelteon as directed in the Hetlioz label it will
18 lead to the practice of Claim 3 of the '604 patent?

19 A. Yeah. He stated that if you're prescribing
20 tasimelteon, you would know that it would necessarily be
21 resulting in treatment.

22 Q. If the Court were to accept that position, would you
23 conclude that the remaining limitations of the claim, the
24 ones that are in the preamble, are disclosed by the clinical
25 trials reference?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Yes, definitely. So in other words, if, again, what
2 comes after the patent on the right here, the label, is
3 going to necessarily infringe on the patent in terms of
4 entrainment, then clinicaltrials.gov tells you to do the
5 exact same thing and, therefore, would anticipate what's in
6 the patent.

7 Q. And so, just for clarity of the record, do the
8 clinical trials referenced in the Hetlioz label both
9 disclose Non-24 Sleep-Wake Disorder?

10 A. Yeah, they both, again, in blue 20-milligram dose of
11 tasimelteon, yes.

12 Q. And do they both disclose administering at a half
13 hour to an hour and a half before bedtime?

14 A. Yes. In the green, they both talk about
15 approximately an hour prior to bedtime.

16 Q. And do they both disclose that the patients were
17 totally blind?

18 A. Again, in purple, both disclose that these were
19 totally blind patients.

20 Q. That takes care of our first and by far longest
21 patent. So let's now move to the next one, the '829 patent.

22 Dr. Emens, could you summarize your invalidity
23 opinions on Claim 14 of the '829 patent?

24 A. Yeah. As invalid as obvious over the combination of
25 Lankford, Hack, the '244 publication and Hardeland, as well

DIRECT EXAMINATION - JONATHAN EMENS

1 as obvious over the combination of Hardeland, Hack, and the
2 '244 publication.

3 Q. And in analyzing the validity of Claim 14 of the '829
4 patent, did you also consider the limitations of Claim 13?

5 A. I did.

6 Q. And so Claim 14, does it have anything in common with
7 Claim 3 of the RE604 patent that we were just looking at?

8 A. Yeah. So you can see highlighted in yellow, they
9 both discuss the treating of individuals with Non-24 and
10 also in blue using tasimelteon at a dose of 20 milligrams.

11 Q. And so those limitations that are common to the two
12 patents, why would those have been obvious in view of the
13 two combinations of prior art references that you've set
14 forth?

15 A. So for the same reasons I already explained about
16 Claim 3 of the RE604 that would be obvious.

17 Q. And does Claim 14 of the '829 patent add anything
18 that's not in Claim 3 of the '604 patent?

19 A. Yes. So it adds that prior to starting treatment of
20 tasimelteon, that you would discontinue treatment with a
21 strong CYP1A2 inhibitor, such as Fluvoxamine.

22 Q. And what did you rely on in concluding that this
23 additional limitation would have been obvious in light of
24 the two combinations of prior art references that you've set
25 forth?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. So obvious over Lankford, Hack, the '244 publication
2 and Hardeland, as well as obvious over this combination of
3 Lankford, Hack and the '244 publication.

4 Q. And regarding this additional limitation that
5 requires discontinuing a strong CYP1A2 inhibitor before you
6 administer tasimelteon, what did you rely on to conclude
7 that that additional limitation would have been obvious as
8 well?

9 A. So I relied on the report of Dr. Greenblatt. Again,
10 given his expertise in pharmacokinetics and CYP3A4-related
11 drug interactions, and I relied on his report.

12 Q. Let's now move to our next patent, the '910, and
13 specifically Claim 4.

14 Could you summarize your conclusions on the
15 validity of Claim 4 of the '910?

16 A. Yeah. Obvious over the combination of Lankford,
17 Hack, the '244 Publication, Pandi-Perumal, as well as
18 obvious over Hardeland, Hack, the '244 Publication and,
19 again, Pandi-Perumal.

20 Q. All right. Let's do something similar with this
21 claim. Does Claim 4 of the '910 patent have anything in
22 common with Claim 3 of the RE604 patent that we were just
23 looking at?

24 A. It does.

25 Q. And what are those commonalities?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Again, using the same color-coding scheme, Claim 4 of
2 the '910 patent talks about the treatment of Non-24, which
3 is, again, seen in the RE604 patent, and also in yellow on
4 the left. It talks about treating these individuals using a
5 20-milligram dose of tasimelteon, both in blue for both of
6 these, and that these would be totally blind individuals;
7 and highlighted in purple, light-perception impaired I take
8 to be synonymous with blind.

9 And, finally, the administration time is the
10 same in the Claim 4 of the '910 patent. It's once daily
11 before target bedtime. Again, we see that in Claim 3 of the
12 RE604 patent. Administered half an hour to an hour and a
13 half before bedtime, or in the Claim 1, once daily before
14 targeted bedtime; highlighted, again, in green.

15 Q. And so these limitations that are common to both
16 patents, why would those limitations have been obvious in
17 light of the prior art combinations that you've described
18 for us today?

19 A. Yeah, again, for the same reasons of why I stated
20 earlier why Claim 3 of the RE604 would have been obvious.

21 Q. And does Claim 4 of the '910 patent add anything
22 that's not in Claim 3 of the RE604 patent?

23 A. Yeah. So it specifies prior to treating with
24 tasimelteon that you want to discontinue Rifampin, which is
25 a CYP3A4 inducer, to avoid that particular drug-drug

DIRECT EXAMINATION - JONATHAN EMENS

1 interaction.

2 Q. And what did you rely on in concluding that this
3 additional limitation of Claim 4 is invalid in light of your
4 two obviousness combinations?

5 A. Again, I really relied on Dr. Greenblatt's report
6 based on his expertise as a pharmacologist.

7 Q. All right. That gets us to our last patent, the '487
8 patent. I'd like to begin with obviousness.

9 Could you summarize your opinions on the
10 obviousness of Claim 5 of the '487 patent?

11 A. Yeah. So it would be obvious over the combination of
12 Lankford, Hack, and the '244 Publication, as well as the
13 combination of Hardeland, Hack, and the '244 Publication.

14 Q. And are those the same two combinations that you used
15 when you were discussing Claim 3 of the RE604 patent?

16 A. They are.

17 Q. And analyzing the validity of Claim 5 of the '487
18 patent, did you also look at Claims 1 and 4?

19 A. I did.

20 Q. All right. Does Claim 5 have any similarities to
21 Claim 3 of the RE604 patent?

22 A. Yeah. So as we saw before, Claim 5 of the '487
23 patent, similar to Claim 3 of the RE604 patent, in yellow
24 both are talking about treating individuals with the
25 circadian rhythm disorder, Non-24.

DIRECT EXAMINATION - JONATHAN EMENS

1 They both talk about administering a dose of
2 tasimelteon of 20 milligrams daily, in blue.

3 Q. And does Claim 5 add anything that's not in Claim 3
4 of the RE604 patent?

5 A. Yes, it adds you would be administering tasimelteon
6 without food.

7 Q. So this additional limitation requiring that the
8 tasimelteon is administered without food, in your opinion
9 would that have been obvious?

10 A. Yes.

11 Q. And could you explain to the Court why that is?

12 A. So I relied on the Court's claim construction, so
13 that "without food" means patient had no food within
14 30 minutes of getting the tasimelteon. And since the
15 tasimelteon, as you can see highlighted in orange, the MA-1
16 is being administered 30 minutes prior to bedtime, I think
17 the likelihood -- it's more likely than not that they
18 wouldn't have had any food on board.

19 I mean, they, in essence, have two choices. It
20 could be administered with food at that time of the evening
21 or it could be administered without food. And I think it's
22 more likely that they would have been administered without
23 food.

24 Q. And you culled out a portion from the -- I believe
25 the '244 Publication at DTX-41.10 that talks about

DIRECT EXAMINATION - JONATHAN EMENS

1 administering 30 minutes prior to bedtime; is that right?

2 A. I did, yes.

3 Q. So to sum up, do the two combinations of Lankford,
4 Hack, and the '244 Publication, and Hardeland, Hack, and the
5 '244 Publication collectively disclose each limitation of
6 Claim 5 of the '487 patent?

7 A. They do.

8 Q. And finally on to our last issue, let's go to written
9 description.

10 To start with, as the standard has been
11 explained to you by the lawyers, what do you understand the
12 written description requirement to mean?

13 A. Yeah. So in lay terms what was explained to me was
14 that an inventor has to give you enough detail to know that
15 you had possession of the invention; in other words, that
16 you actually invented what you're claiming to invent.

17 Q. Okay. So let's -- I'd like first to just focus on
18 the right side of the slide, which is the actual language of
19 Claim 5.

20 So in your opinion, does Claim 5 of the '487
21 patent require that administering tasimelteon without food
22 be better at treating Non-24 than administering it with
23 food?

24 A. No.

25 Q. Why not?

DIRECT EXAMINATION - JONATHAN EMENS

1 A. Because it does haven't any -- it doesn't say
2 anything about that. It doesn't say anything about being
3 more effective if you give it without food. It's not in the
4 patent.

5 Q. And were you in the courtroom when Dr. Polymeropoulos
6 testified?

7 A. I was.

8 Q. And did you hear him suggest that Vanda invented a
9 method of administering tasimelteon without food that's more
10 effective at treating Non-24 than if you were to administer
11 it with food?

12 A. I did.

13 Q. So if the Court were to conclude that Claim 5
14 incorporates this notion of improved efficacy in treating
15 Non-24 with tasimelteon without food versus treating Non-24
16 with tasimelteon with food, would that have any implications
17 for your opinions on the validity of Claim 5?

18 A. Yes.

19 Q. And what are those implications?

20 A. It would be invalid for a lack of written
21 description.

22 Q. And could you explain why that is?

23 A. Yeah. There's no data in the patent, or I think
24 anywhere, to suggest that administering tasimelteon without
25 food is any more effective for the treatment of Non-24 than

DIRECT EXAMINATION - JONATHAN EMENS

1 administering it with food.

2 MR. MILLIKEN: And Mr. Brooks, could we switch
3 off the slides and pull up -- I believe it's JTX-5.

4 And if we could just make that a little bit
5 bigger if possible.

6 BY MR. MILLIKEN:

7 Q. And JTX-5, is this the '487 patent that we were just
8 discussing, Dr. Emens?

9 A. Yes, it is.

10 Q. And does the '487 patent -- you can just flip through
11 in your binder. How long is it?

12 A. It's really just two pages back and front. I mean --
13 well, I guess if you include -- I guess four pages total.

14 Q. Okay. And does it have any study results in there,
15 in the specification of the patent?

16 A. Yeah. It talks about the effects of administering
17 tasimelteon to sighted healthy individuals with or without
18 food.

19 Q. Okay.

20 MR. MILLIKEN: And then, Mr. Brooks, if we could
21 go to Page 3 of this document.

22 And if we could blow up the background of the
23 Invention section.

24 BY MR. MILLIKEN:

25 Q. You see there where it says US Patent Application

DIRECT EXAMINATION - JONATHAN EMENS

1 Publication Number 2013/0197076?

2 A. Yes.

3 Q. And I don't expect you to remember the number, but
4 does it sound right that this is the patent application
5 publication that corresponds to the RE604 patent that we
6 were talking about earlier?

7 A. Yes.

8 Q. And does that patent specification contain the
9 results of the SET and RESET studies that Vanda did?

10 A. No.

11 Q. I'm sorry, this is -- we're talking now about the
12 RE604 patent.

13 A. Oh, sorry, sorry. I'm mixing this up with the '244.
14 Yes, it does.

15 Q. And those SET and RESET studies, did those studies
16 study the effect of administering tasimelteon with food
17 versus without food?

18 A. No.

19 Q. What would you need to do to figure out tasimelteon
20 is more effective at treating Non-24 when administered
21 without food than it is administered with food?

22 A. You know, you'd really have to do a head-to-head
23 trial. So you'd have to kind of do the study where you gave
24 the tasimelteon to a group of patients with Non-24 with food
25 and have some matched patients or crossover to the same

DIRECT EXAMINATION - JONATHAN EMENS

1 patents where you then give it with and without food and see
2 if one is more likely to cause treatment success than the
3 other.

4 Q. Thank you very much, Dr. Emens.

5 MR. MILLIKEN: I pass the witness, Your Honor.

6 THE COURT: All right. Do you think we should
7 break for lunch?

8 MR. GROOMBRIDGE: Sure, Your Honor. Half an
9 hour?

10 THE COURT: Half an hour works then. All right.
11 We'll be back in half an hour, thank you.

12 You may step down. And the witness is not on
13 cross yet so he can speak with counsel. Thank you.

14 (Recess taken.)

15 MR. MILLIKEN: Your Honor, one housekeeping
16 matter. I was advised, I neglected to move JTX-5 into
17 evidence, which is the '487 patent. I understand there's no
18 objection.

19 MR. GROOMBRIDGE: Not surprisingly, Your Honor,
20 we're certainly happy to have that in evidence.

21 THE COURT: It's admitted.

22 MR. MILLIKEN: Thank you, Your Honor.

23 (JTX-5 admitted into evidence.)

24 CROSS-EXAMINATION

25 BY MR. GROOMBRIDGE:

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. Dr. Emens, good afternoon again.

2 A. Good afternoon.

3 Q. I'd like to start with a paper that you wrote.

4 Let's put up -- can you open the white binder, please, and
5 you should find, first of all, there's a copy of your
6 deposition and the next thing should be PTX-005.

7 A. Yes, I'm there.

8 Q. And that's a review article titled: Diagnosis and
9 Treatment of Non-24-Hour Sleep-Wake Disorder in the Blind;
10 correct?

11 A. Yes.

12 Q. And there are two authors and you're the first one,
13 correct?

14 A. Yes.

15 Q. And the other author is someone named Charmane
16 Eastman, who is also a well-known researcher in your field,
17 correct?

18 A. Yes, she is.

19 Q. And, in fact, I believe we have heard she was one of
20 the people on the advisory committee that recommended
21 approval of tasimelteon, correct?

22 A. Oh. Yes, I have to admit I don't know for sure that
23 she was on the advisory committee, but I'll definitely take
24 your word for it.

25 Q. And is this an article that you wrote in 2017

CROSS-EXAMINATION - JONATHAN EMENS

1 summarizing things that were known in the field and how the
2 field had developed over time?

3 A. Yes.

4 MR. GROOMBRIDGE: Your Honor, we would offer
5 PTX-5 into evidence.

6 MR. MILLIKEN: No, objection.

7 THE COURT: All right. It's admitted.

8 (PTX-5 admitted into evidence.)

9 MR. GROOMBRIDGE: Put up Page 5, please.
10 Start by enlarging that text, please.

11 BY MR. GROOMBRIDGE:

12 Q. And just -- Dr. Emens, just in case this is an
13 important thing, there may have been some question about the
14 prevalence of Non-24. Here, in the beginning of the
15 abstract, you say that it's a disorder occurring in 55 to
16 70 percent of totally blind individuals. Is that right?

17 A. Yes.

18 Q. And is that information generally accurate?

19 A. Yes.

20 Q. Now, moving down you say: Orally administered
21 melatonin and the melatonin agonist tasimelteon have been
22 shown to entrain (synchronize) the circadian clock,
23 resulting in improvements in nighttime sleep and daytime
24 alertness.

25 Is that correct?

CROSS-EXAMINATION - JONATHAN EMENS

1 A. Yes.

2 Q. And is that an accurate statement?

3 A. Yes.

4 Q. And other than melatonin -- let me withdraw that.

5 You used the phrase in your direct examination a
6 "synthetic melatonin agonist," and I'd like to talk about
7 that a little bit.

8 Now, just to lay the groundwork here, does an
9 agonist mean a drug that causes a certain re- -- hits a
10 receptor in the body and causes a reaction?

11 A. It means a chemical, either endogenous or exogenous,
12 that would act on that receptor, yes.

13 Q. Thank you. And that's a very good point.

14 Melatonin is what we call endogenous because the
15 body itself makes melatonin, correct?

16 A. Well, actually, melatonin can be both exogenous and
17 endogenous.

18 Q. And that's partly what I'm trying to get at here.

19 So we can have endogenous melatonin, which is
20 melatonin made by the body itself, correct?

21 A. Yes.

22 Q. And we could have exogenous melatonin, which would be
23 melatonin that someone took, right, and that's how it got
24 into their body, correct?

25 A. Oh, yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And it's exogenous melatonin that we've been talking
2 about and you were talking about in your direct examination
3 as a treatment for Non-24, correct?

4 A. Yes.

5 Q. And melatonin the molecule is not a synthetic
6 melatonin agonist, as you used the term, correct?

7 A. Just to make sure I understand, do you mean
8 endogenous who produced melatonin molecules, or...

9 Q. Well, when you said -- I think I heard you say, you
10 talked about a synthetic melatonin agonist?

11 A. Yes.

12 Q. Does that mean something other than melatonin itself?

13 A. It means a melatonin that is -- something that's
14 manufactured as opposed to what's made in the body.

15 Q. Now, prior to 2012, had any molecule other than
16 melatonin itself been shown to entrain the circadian clock
17 and thereby resulted in improvements to nighttime sleep and
18 daytime alertness?

19 A. In Non-24?

20 Q. In Non-24.

21 A. No.

22 Q. And so when you were writing this article, the only
23 ones that had been shown to have that ability were melatonin
24 and tasimelteon, correct?

25 A. Yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And prior to the publication of the results of the
2 SET and RESET studies, had it ever been shown in the field
3 that tasimelteon could entrain Non-24 patients?

4 A. Not prior to the publication of the results of the
5 trial, no.

6 Q. And now am I right that the reason that you spent
7 some time on your direct examination going through what we
8 might be able to call the melatonin prior art is because in
9 your opinion, that provides a meaningful teaching to the
10 skilled person that they could apply to the use of
11 tasimelteon; is that fair?

12 A. Yes.

13 Q. And in terms of dosage, is it -- can we read across
14 from a particular dose of milligrams of melatonin to have an
15 idea of what kind of dose of tasimelteon we should give
16 someone?

17 A. As you and I talked about in my deposition, it's not
18 necessarily a one-to-one correlation.

19 Q. Is there -- I'm sorry, did you finish?

20 A. Yeah, no. Please go ahead.

21 Q. Is there any correlation at all?

22 A. I apologize for hesitating.

23 There's no, say, dose response curve for the
24 resetting effects of tasimelteon that I could compare to,
25 say, what we constructed for melatonin in quite the same

CROSS-EXAMINATION - JONATHAN EMENS

1 way. So it's hard to kind of answer that question.

2 I mean, I think, to be fair, I think you're
3 right that I suppose we can make some inferences from one
4 dose to the other, but since they're different molecules,
5 it's hard to kind of make a milligram, say, equivalent
6 comparison, if that makes sense.

7 Q. And I think you previously said to me that for some
8 categories of drugs, like --

9 A. We talked about opiates.

10 Q. Opiates, yes.

11 That you could figure out how much of a standard
12 like morphine they were equivalent to, correct?

13 A. Exactly, yes.

14 Q. And that way you could, from one opiate to another,
15 you could say, well, if X milligrams of this one works, then
16 I know that probably Y milligrams of this one will work.

17 Is that fair?

18 A. Yes.

19 Q. But that's not possible between melatonin and
20 tasimelteon, correct?

21 A. Yeah, the studies haven't been done.

22 Q. And even as of today, no study has been done that
23 would make that possible, correct?

24 A. No head-to-head trials comparing the two, yes.

25 Q. Now, Dr. Emens, you're familiar, very familiar, with

CROSS-EXAMINATION - JONATHAN EMENS

1 the concept of a phase response curve for melatonin, are you
2 not?

3 A. Yes.

4 Q. And you have, yourself, published quite a bit about
5 that, correct?

6 A. I have published not experiments and constructing
7 response curves, but definitely I have talked about these
8 response curves, yes.

9 MR. GROOMBRIDGE: And let's go, if we could, to
10 Page 4 of Exhibit 5.

11 THE WITNESS: Yes, I am there.

12 BY MR. GROOMBRIDGE:

13 Q. By the way, I should have asked at the beginning, but
14 what is the purpose of a so-called review article?

15 A. Well, it's really to kind of synthesize the state of
16 the field, you know, what's the current knowledge base.

17 Q. And in this review article, is the intended audience
18 researchers and treating physicians in your field?

19 A. Yes, I think it's fair to say both.

20 MR. GROOMBRIDGE: And if we go to Page 4, let's
21 enlarge the text in the lower left-hand corner, please.

22 BY MR. GROOMBRIDGE:

23 Q. And when you use the term "PRC," it means phase
24 response curve, correct?

25 A. Yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And in Figure 1, we'll come to that in a moment, but
2 it says: These PRCs illustrate the striking fact that the
3 same dose of melatonin can have opposite effects on the
4 circadian clock, depending on the biological time of
5 administration.

6 And that's accurate, correct?

7 A. Oh, yes.

8 Q. And, you go on to say that -- that melatonin
9 administered in the afternoon and early evening resets the
10 clock to an earlier hour. It advances it, correct?

11 A. Correct.

12 Q. And when we say "reset the clock," you're talking
13 about the master body clock, right?

14 A. Yes.

15 Q. And by contrast, if we take melatonin in the morning,
16 it would have the opposite effect; it would delay the clock,
17 correct?

18 A. Yes.

19 Q. And people in your field have plotted this out
20 graphically, right?

21 A. Yes.

22 MR. GROOMBRIDGE: If we take this down and put
23 up Figure 1.

24 BY MR. GROOMBRIDGE:

25 Q. That's what Figure 1 shows, correct?

CROSS-EXAMINATION - JONATHAN EMENS

1 A. Yes, that's exactly what it shows.

2 Q. Depending on when I take the melatonin, it will
3 either pull my rhythm forward or push it backward, correct?

4 A. Yes. And I would say when I take it relative to my
5 body clock, not to clock hour.

6 Q. And "body clock" meaning the intrinsic circadian
7 rhythm?

8 A. Yes, correct.

9 Q. And as Figure 1 shows, the exact phase response curve
10 would also vary depending upon the dose that has been given,
11 would it not?

12 A. Yes. In this case there were slight differences when
13 Drs. Eastman and Burgess administered 0.5 versus 3
14 milligrams in the phase response curves that they got. They
15 were pretty similar, though, but slight differences.

16 Q. And would tasimelteon also have an effect whereby it
17 can either pull the clock forward or push it backward
18 depending upon time of administration?

19 A. I would expect that, yes.

20 Q. But even as of today, no one has actually ever
21 published that, correct?

22 A. Correct.

23 Q. Even as of today, there has never been, in the
24 literature, a phase response curve for tasimelteon?

25 A. That's definitely correct, yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. Now, let me ask, would you agree that -- that a
2 lot -- many years of work was spent by your people in the
3 field trying to establish whether melatonin could affect
4 so-called phase shifts in human beings?

5 A. Yeah. I mean, I would -- many years, that work
6 really is in the '80s and early '90s. So, you know, maybe
7 over a decade period of time, people were demonstrating that
8 melatonin could cause phase shifts, so that might be many
9 years.

10 MR. GROOMBRIDGE: Let's look at Page 5, please.

11 And let's enlarge the first paragraph under
12 section heading 5.

13 BY MR. GROOMBRIDGE:

14 Q. And this is headed: Initial Demonstration of
15 Melatonin Treatment of Non-24 and Concept of Spillover,
16 correct?

17 A. Yes.

18 Q. And we'll come to spillover in a minute, but that's
19 something that you have written about fairly extensively; is
20 that correct?

21 A. Yes, that's correct.

22 Q. And here, reviewing the history, you say that:
23 Melatonin was shown to be capable of entraining free-running
24 rats in 1983, correct?

25 A. Correct.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. All right. But nonetheless, it took another 17 years
2 until it was shown that it was capable of entraining the
3 circadian rhythm of blind human beings, correct?

4 A. Yes, that's correct.

5 Q. And you mentioned, you see there it's commonly
6 accepted that there were two publications that came out very
7 close in time that --

8 A. Yes.

9 Q. -- that showed that, correct?

10 A. Yes.

11 Q. And one of them -- I think you talked about both of
12 them in your direct examination, did you not?

13 A. I did.

14 Q. And one of them is a paper in which the first author
15 is Dr. Lockley, correct?

16 A. Yes.

17 Q. And the Court will be hearing from Dr. Lockley very
18 soon, I think.

19 And the other one is a paper in which the first
20 author is someone called Dr. Sack, correct?

21 A. That's correct.

22 Q. And Dr. Sack was a researcher in the institution
23 where you now work, correct?

24 A. Yes, that's correct.

25 Q. And it was a big deal in your field when those two

CROSS-EXAMINATION - JONATHAN EMENS

1 papers came out, was it not?

2 A. Yes, definitely.

3 Q. Dr. Sack's paper was in the New England Journal of
4 Medicine and attracted a lot of attention.

5 A. Yes, definitely.

6 Q. And over the years, Dr. Lockley's paper has attracted
7 a lot of attention too; is that right?

8 A. Yes, I would say so.

9 Q. Now, would you agree, then, looking at that history
10 that a skilled person would have known that merely because a
11 particular molecule can entrain animals such as rats, it
12 doesn't necessarily follow that it can entrain human beings?

13 A. Yes, I'd agree. Just because it can entrain one
14 species doesn't guarantee that it would entrain other
15 species.

16 Q. And the -- and now I'd like to talk a little bit
17 about spillover.

18 MR. GROOMBRIDGE: Let's take that down, please.

19 And, Mr. Weir, let's enlarge the last paragraph
20 on the right-hand side.

21 BY MR. GROOMBRIDGE:

22 Q. Do you see here where -- you're talking about the
23 fact here that sometimes a larger dose of melatonin is less
24 effective than a smaller dose at entraining people, correct?

25 A. Correct.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And you have hypothesized that the reason for that is
2 that the melatonin remains present in the body long enough
3 that it's still there when you reach the delay part of the
4 phase response, correct?

5 A. Yes, that's exactly correct.

6 Q. And so, one of the things that follows from that is
7 it matters significantly if one wishes to achieve
8 entrainment how much of the drug is administered, correct?

9 A. Yes, definitely dose affects whether you would expect
10 to get spillover, exactly true.

11 Q. And, similarly, it matters when the drug is
12 administered, correct?

13 A. Yes.

14 Q. And that's because the closer in time one is to the
15 crossover point from advance to delay on the phase response
16 curve, the more likely that it will end up having delay
17 effects, correct?

18 A. Yes. And just to clarify, when we're talking about
19 when you said "time," again, biological time, not clock
20 hour.

21 Q. Correct, right.

22 And for any given individual, we -- particularly
23 someone with Non-24, we may not know how their internal
24 circadian time matches the rest of the world's clock time,
25 correct?

CROSS-EXAMINATION - JONATHAN EMENS

1 A. Exactly, yes.

2 Q. Without doing some form of evaluation, it's probably
3 not possible to know that, correct?

4 A. Yeah, you would have to do an assessment of circadian
5 phase. You'd have to measure, in other words, what time it
6 was in their body.

7 Q. And the term that -- did you coin the term
8 "spillover"?

9 A. It was coined in an article in 2002 that Al Lewy and
10 I wrote together so I would think we'd give credit to Al
11 Lewy.

12 Q. Perhaps you're being modest, Doctor, but certainly
13 you were one of the authors on the paper that brought this
14 term into the field?

15 A. Yes, I was.

16 Q. And here when talking about that you say: Higher
17 doses can spill over onto the wrong portion of the melatonin
18 PRC.

19 Do you see that?

20 A. I do.

21 Q. And you said that you can, in fact, get a dose that's
22 high enough that it's incapable of producing the phase shift
23 necessary for entrainment, correct?

24 A. Yes.

25 Q. And that's because there would be so much of the

CROSS-EXAMINATION - JONATHAN EMENS

1 agent, in this case the melatonin, present that you would
2 never reach a point where it was not active in the phase
3 delay part of the curve, correct?

4 A. Well, if you had a high enough dose, you would be
5 getting both kind of helpful phase advances and unhelpful
6 phase delays, as we were talking about before, and they
7 counteract each other.

8 Q. They counteract each other, right?

9 A. Exactly.

10 Q. And that's what you are talking about when you say in
11 Exhibit 5, that you're talking about the net amount of
12 resetting, correct?

13 A. Precisely, yes.

14 Q. And what you're saying is I get a big positive amount
15 when the patient takes this and I'm on the advance part of
16 the curve, but then I get a pretty big negative effect on
17 the delay side of the curve and the overall result is a very
18 small or no shift, correct?

19 A. Exactly.

20 Q. Let's go to Page 6, please. Let's enlarge the
21 paragraph under the Section 5.2.

22 Here you're talking about entrainment with
23 melatonin at the correct time; is that right?

24 A. Yes.

25 Q. And you say: One unique feature of treating Non-24

CROSS-EXAMINATION - JONATHAN EMENS

1 is the fact that it is important to not just stop the clock
2 from free running, but to entrain it at the proper time
3 relative to the desired time for sleep.

4 Correct?

5 A. Yes.

6 Q. And if we look at that, when you say "unique
7 feature," what you mean there is that this is different from
8 treating other circadian rhythm disorders, correct?

9 A. Well, to be fair, for other circadian rhythm sleep
10 disorders you would also want to entrain -- I mean reset
11 their clock to the proper time, too. So if someone had,
12 say, delayed sleep phase disorder, so their clock is set too
13 late, it's not just a point of resetting them earlier. I
14 want to set them earlier enough to get them to the correct
15 time.

16 Q. For example, if I look at, say, jet lag, someone who
17 is suffering from jet lag, what I want to do is pull them on
18 to the right time, but once I've done that, I don't need to
19 worry about them staying there, correct?

20 A. So that's -- yeah, it would be a different point in
21 terms of maintenance versus putting them to the right time.

22 Q. And by the way --

23 MR. GROOMBRIDGE: You can take that down,
24 Mr. Weir --

25 THE COURT: By the way, I just want to -- I

CROSS-EXAMINATION - JONATHAN EMENS

1 should tell all witnesses, but I'm looking at a display
2 here. So if I'm looking at you and looking down here, just
3 so you understand why I'm not -- I'm staring at something,
4 actually.

5 THE WITNESS: Thank you.

6 BY MR. GROOMBRIDGE:

7 Q. Doctor, in this article, and this is published in
8 2017, did you call into question the fact that even at that
9 point it might, in your opinion, be that 20 milligrams was
10 not the best dose of tasimelteon in order to treat Non-24?

11 A. Yes.

12 Q. And you said in this article that -- that you're
13 positive that perhaps 10 milligrams would be the better
14 dose, correct?

15 A. Can you point me to where you're --

16 Q. I certainly can. Let's go to Page 8 and let me know
17 when you've got that.

18 A. I'm there.

19 Q. And you see there's a section here "Tasimelteon for
20 the Treatment of Non-24"?

21 A. Yes.

22 Q. And let's just take a look at that. At the very
23 bottom, in fact, the last half line of the left-hand column,
24 you start talking about the SET trial, right?

25 A. Yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And then you go on talking about that in the upper
2 column.

3 MR. GROOMBRIDGE: And Mr. Weir, let's see if we
4 can get those up on the screen, please.

5 BY MR. GROOMBRIDGE:

6 Q. And here you're talking about SET and RESET.

7 A. Yes.

8 Q. And you note that in the SET trial, tasimelteon
9 entrained 8 out of 40 or 20 percent of the patients after
10 four weeks of treatment, correct?

11 A. Yes.

12 Q. And you say the RESET trial, that it entrained
13 50 percent of the patients after 12 to 18 weeks, correct?

14 A. Yes.

15 Q. And you go on to refer to some data suggesting that
16 after seven months of tasimelteon treatment, 59 percent of
17 people would be entrained, correct?

18 A. Yes.

19 Q. And so would it be fair to conclude that in order to
20 know how good a particular molecule is at entraining blind
21 people, one of the things that could be important is how
22 long the course of treatment was?

23 A. Yes.

24 Q. And is that partly because, for any given individual,
25 it may depend upon how long it takes until the drug is, in

CROSS-EXAMINATION - JONATHAN EMENS

1 your words, hitting the right time of their internal cycle?

2 A. Yes, exactly.

3 Q. So if I'm someone with a tau, an internal circadian
4 rhythm that's only a little bit over 24 hours, it'll take me
5 a relatively long time, could be several months, to cycle
6 around the clock?

7 A. Indeed, yes.

8 Q. And if I start being treated for Non-24, be it with
9 melatonin or tasimelteon, I may not entrain until weeks or
10 months into the treatment when finally the time of day when
11 I'm taking the drug hits the right part of my internal
12 circadian rhythm, correct?

13 A. Yes, you're exactly right.

14 Q. And just --

15 MR. GROOMBRIDGE: We can take that down here.

16 BY MR. GROOMBRIDGE:

17 Q. One more thing I'd like to look at before we move on.
18 I think it's only one more thing.

19 Let's go to Page 9, please.

20 MR. GROOMBRIDGE: And Mr. Weir, let's enlarge
21 the last paragraph in this section.

22 BY MR. GROOMBRIDGE:

23 Q. And at the end of this you say: The peak
24 concentration of tasimelteon was cut to about half when
25 taken with a high-fat meal.

CROSS-EXAMINATION - JONATHAN EMENS

1 Correct?

2 A. Yes.

3 Q. And what you're talking about there is one of the
4 publications that reported the effects of Vanda's work on
5 so-called -- the food effect study; isn't that right?

6 A. Yes.

7 Q. And you then go on to propose: This might be a way
8 to reduce the dose and allow it to be taken earlier without
9 causing too much sleepiness.

10 Correct?

11 A. Yes.

12 Q. What you're saying there is that tasimelteon itself
13 can act as soporific, right, in addition to its circadian
14 rhythm resetting properties?

15 A. Exactly, yes.

16 Q. And so if I take it at an hour before a target
17 bedtime, that may not matter too much because I'm planning
18 on going to bed, correct?

19 A. Oh, are you asking me whether there wouldn't be a
20 food effect?

21 Q. Terrible question. Let me try again.

22 A. Sorry.

23 Q. One of the things that you've posited is that in at
24 least some circumstances it's preferable to use a lower
25 dose, for example, of melatonin that can be given earlier in

CROSS-EXAMINATION - JONATHAN EMENS

1 the day so it won't compromise the patient's ability to
2 engage in activities of daily living, like driving, for
3 example.

4 Is that fair?

5 A. Yes.

6 Q. All right. And here what you're saying is that by
7 analogy or -- you might be able to do the same thing with
8 tasimelteon and to take a smaller dose earlier in the day,
9 by taking advantage of the so-called food effect; is that
10 fair?

11 A. Yes.

12 Q. I would like to now move on and go through some of
13 the melatonin art and I'm going to try to keep it to a
14 minimum, but hopefully we can not be too onerous here.

15 I'd like to go now to look at a document called
16 PTX-283.

17 And can you turn to that. Should be the next
18 item in the binder.

19 A. Yes, I'm there.

20 Q. And are you familiar with this publication?

21 A. Yes, I haven't looked at it recently, but I do know
22 of it.

23 Q. It's an older publication from 1991, is it not?

24 A. Yes.

25 Q. And it's by Dr. Sack and Dr. Lewy and a number of

CROSS-EXAMINATION - JONATHAN EMENS

1 other colleagues at the institution at which you now
2 practice, right?

3 A. Yes.

4 MR. GROOMBRIDGE: Your Honor, at this point, we
5 offer Plaintiff's Exhibit 283 into evidence.

6 MR. MILLIKEN: No objection.

7 THE COURT: It's admitted.

8 (Plaintiff's Exhibit 283 admitted into
9 evidence.)

10 MR. GROOMBRIDGE: And let's just -- Mr. Weir,
11 please put up the title and we'll enlarge the title
12 information. Let's get the header as well so we have the
13 date, please.

14 BY MR. GROOMBRIDGE:

15 Q. Again, just make sure we're all on the same page,
16 this is a publication titled "Melatonin Administration to
17 Blind People: Phase Advances and Entrainment."

18 Doctor, what's a phase advance? Is that the
19 concept we were talking about, for example, with jet lag
20 where we pull the circadian rhythm forward?

21 A. Yeah, it refers to shifting what time it is in your
22 body. So if I wanted to measure what time it was in your
23 body, although there's been a lot of talk about the dim
24 light melatonin onset. And so a phase advance would be
25 shifting the timing of when my melatonin rises to an earlier

CROSS-EXAMINATION - JONATHAN EMENS

1 time. And all the rhythms are thought to be yoked together
2 so they would all shift to an earlier time. And that would
3 be a phase advance. Exactly.

4 Q. And I could have a phase delay where all the rhythms
5 get pushed to a later time, correct?

6 A. Yes, exactly.

7 Q. And those two together, phase advance and phase
8 delay, collectively would be termed "phase shifting"?

9 A. Yes.

10 Q. And would you agree that the ability of a particular
11 drug to phase shift is a necessary but not sufficient
12 condition for it to be able to entrain?

13 A. That is correct.

14 Q. And would you agree that in this paper, Dr. Sack and
15 his colleagues report that they were able to produce --
16 well, let me withdraw that. Let us look at it in fairness
17 to you.

18 Let's go to Page 10, please.

19 MR. GROOMBRIDGE: Mr. Weir, when you get there,
20 let's enlarge the second full paragraph here, please. The
21 one beginning -- no, second full paragraph, third paragraph.
22 There we go.

23 BY MR. GROOMBRIDGE:

24 Q. And here Dr. Sack and his colleagues say: Although
25 we were able to produce robust phase advances in four of our

CROSS-EXAMINATION - JONATHAN EMENS

1 five subjects, we were not able to entrain them.

2 Would you agree that a person of skill would
3 know that it may be possible to produce a phase advance, but
4 not possible to achieve entrainment?

5 A. Yes.

6 Q. Let's go on to -- let's go to -- move on. I think
7 it's two tabs in the binder. And let's get to JTX-123,
8 which is already in evidence.

9 A. Yes, I'm there.

10 Q. And this is one of the papers you talked about on
11 your direct examination, is it not?

12 A. Correct.

13 MR. GROOMBRIDGE: Let's put that up, Mr. Weir,
14 when you get a chance. And let's enlarge the title.

15 BY MR. GROOMBRIDGE:

16 Q. And you're the second author on this paper, right?

17 A. Correct.

18 Q. And you published it in 2002?

19 A. Yes.

20 Q. And here you say: Low, but not high, doses of
21 melatonin entrained a free-running blind person with a long
22 circadian period.

23 Were the low doses 0.5 milligrams or
24 thereabouts?

25 A. Yeah. 0.5 milligrams was successful in entraining

CROSS-EXAMINATION - JONATHAN EMENS

1 the one individual I talked about earlier in this article.

2 Q. And the high doses you tried here were 10 and
3 20 milligrams?

4 A. 10 and 20, correct.

5 Q. And let's go to Page 5 of the document where you talk
6 about that.

7 MR. GROOMBRIDGE: And let's enlarge the last ten
8 lines or so, please, Mr. Weir.

9 BY MR. GROOMBRIDGE:

10 Q. Here you're positing, again, that spill over is the
11 culprit, correct?

12 A. Yeah, this is where we first proposed the idea of
13 spill over.

14 Q. And what you're saying is that in instances where you
15 couldn't achieve entrainment, you hypothesized the larger
16 melatonin dose the more likely it will spill over into the
17 wrong zone of the PRC; is that right?

18 A. That is correct, yeah.

19 Q. And a skilled person in the field would have known of
20 your work saying that perhaps you need a lower dose rather
21 than a higher dose if what you wish to do is entrain; fair?

22 A. Yes. I think the one qualification I might say is
23 that within a particular range. So in other words, they
24 would have known, hey, as you get higher, you would get
25 smaller phase shifts, and as you got lower, you would also

CROSS-EXAMINATION - JONATHAN EMENS

1 potentially get lower phase shifts. So on either end of
2 that window. So not necessarily too low and not necessarily
3 too high as well.

4 Q. Very fair point.

5 It's quite possible you could end up with too
6 low of a dose?

7 A. Exactly, yes.

8 Q. And let's turn now to the next item in the book,
9 which should be JTX-146. And this also is already in
10 evidence.

11 Doctor, do you have that?

12 A. I do.

13 Q. And is this the so-called Hack paper?

14 A. It is.

15 Q. And this is one of the references that you rely on in
16 your obviousness combinations, is it not?

17 A. It is.

18 Q. And just so we're clear, this talks about entrainment
19 of people with Non-24, correct?

20 A. Yes, totally blind people with Non-24.

21 Q. And I think you said this in your direct, but just so
22 we're clear, when it says free-running circadian rhythms of
23 blind subjects, that's a terminology that refers to Non-24?

24 A. Yes.

25 Q. And is it correct that that terminology used to be

CROSS-EXAMINATION - JONATHAN EMENS

1 more common, but now Non-24 has displaced it somewhat?

2 A. Yes.

3 Q. This was published in 2003; is that correct?

4 A. Yes.

5 Q. And there's no mention of tasimelteon in this paper,
6 is there?

7 A. No.

8 Q. Let's just go, please, to Page 6.

9 MR. GROOMBRIDGE: And Mr. Weir, let's enlarge
10 Table 3, which appears on the lower right.

11 BY MR. GROOMBRIDGE:

12 Q. Now, Dr. Emens, one of the things you talked about in
13 your direct examination was this table, and specifically the
14 line about total night sleep duration; fair?

15 A. Yes.

16 Q. And you -- what you showed here was that the subject
17 taking placebo in this instance and -- the subjects had a
18 mean of 5.99 hours of sleep per night, correct?

19 A. Yes.

20 Q. And subjects taking melatonin had a mean of 6.64
21 hours of sleep per night, correct?

22 A. Correct.

23 Q. And you were pointing to this in reference to your
24 opinions about a daily sleep period of approximately 7 to
25 9 hours being obvious, correct?

CROSS-EXAMINATION - JONATHAN EMENS

1 A. Correct.

2 Q. Now, this doesn't tell you anything about how much
3 these subjects would have slept had they been taking
4 tasimelteon, correct?

5 A. No.

6 Q. And as with dosage, there would be no way to tell
7 from sleep results attributable to taking melatonin how that
8 might be translated to sleep results from taking
9 tasimelteon; do you agree?

10 A. I would agree, yes.

11 Q. Let's look at the next page.

12 MR. GROOMBRIDGE: And let's enlarge the text on
13 the lower right.

14 BY MR. GROOMBRIDGE:

15 Q. Here you're talking about --

16 A. This isn't --

17 Q. -- dose effect --

18 A. This isn't my paper.

19 Q. I'm sorry? I'm sorry. You're right. This is
20 Dr. Hack and Dr. Lockley. I'm sorry.

21 A. Just to clarify, sorry. I didn't mean to interrupt.

22 Q. No, not at all.

23 The -- here Dr. Hack and her colleagues are
24 talking about dose effects, correct?

25 A. Can you point again to where you're looking?

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1 Q. Yeah. If we look, one explanation for the lack of a
2 clear dose-dependent effect. In the middle of the text we
3 have on the screen.

4 A. I see that, yes.

5 Q. And would you agree with the statement in the Hack
6 paper that melatonin pharmacokinetics are known to vary
7 greatly between individuals?

8 A. Yes.

9 Q. And this talks about the melatonin -- the number and
10 sensitivity of melatonin receptors, correct?

11 A. Yes, it's saying -- it's speculating that there might
12 be differences there.

13 Q. And the melatonin receptors, would you agree that
14 there are two receptors in the body that are called
15 melatonin receptors?

16 A. There are two melatonin receptors that are relevant
17 for our discussion about entrainment, the MT1 and the MT2
18 receptors.

19 Q. Being a scientist, you're being very precise.

20 Fair to say that there are other receptors in
21 the body to which melatonin may bind, but we don't think
22 they are important for the subjects that you're talking
23 about here?

24 A. Correct, yes.

25 Q. But there are two that melatonin -- two melatonin

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1 receptors that melatonin itself binds to, correct?

2 A. Yes.

3 Q. And they're conventionally called MT 1 and MT 2?

4 A. Yes.

5 Q. And is it correct that it's still not fully
6 understood what role those play, which of the two is
7 important for which physiological result?

8 A. Yes, I think it's fair to say there's still some
9 debate. I mean, there's some thought that maybe the MT 1
10 receptors play a greater role in phase shifting. MT 2 maybe
11 plays a greater role in promotion of non-REM sleep.

12 But, yes, that, again, is getting a little bit
13 outside my wheelhouse there. But, yes, I would agree with
14 you.

15 Q. But even as of today in 2022, that's still something
16 that people in your field are researching, correct?

17 A. Yes.

18 Q. And it has been the subject of research for at least
19 20 years, correct?

20 A. Yes.

21 Q. And one of the differences between tasimelteon and
22 melatonin is they have what's called "different affinities"
23 for these two receptors, correct?

24 A. Correct.

25 Q. And they don't just have different absolute

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1 affinities, they have different relative affinities,
2 correct?

3 A. Yes.

4 Q. So tasimelteon binds more strongly to MT 2 and less
5 strongly to MT 1, correct?

6 A. Yes, I believe that's correct.

7 Q. But by contrast, melatonin binds more strongly to MT
8 1 and less strongly to MT 2?

9 A. Yes, I believe that's correct.

10 Q. And that information has been known in the field for
11 quite some time, certainly before 2012, correct?

12 A. Yes.

13 Q. Now I'd like to turn on in the book. I think this
14 is -- let's go to JTX-127, which should be -- I guess it's
15 two tabs further along.

16 A. Yes, I'm there.

17 Q. And -- I'm sorry. Let's go to JTX-94. Should be the
18 next one after what we were just looking at. It's the
19 Ferguson paper.

20 Let me know when you've gotten there.

21 A. Yes, I'm there.

22 Q. And this is one of the exhibits that's in evidence
23 and you testified about this on your direct examination,
24 correct?

25 A. Yes, correct.

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1 MR. GROOMBRIDGE: So Mr. Weir, let's put up the
2 document and enlarge the title and the abstract.

3 BY MR. GROOMBRIDGE:

4 Q. And this was a review article published in 2010,
5 correct?

6 A. Correct.

7 Q. And it's, in essence, Dr. Ferguson and
8 Dr. Rajarantnam and another colleague reviewing the state of
9 the field at this point, correct?

10 A. Yes.

11 Q. So if we will, it's sort of a snapshot of the state
12 of the art in 2010?

13 A. Agreed.

14 Q. And are they talking about various melatonin
15 agonists, not just melatonin itself?

16 A. Yes.

17 MR. GROOMBRIDGE: And let's take that down. And
18 enlarge, please, if we could, Mr. Weir, the top two
19 paragraphs in the right-hand column.

20 BY MR. GROOMBRIDGE:

21 Q. Now, would you agree that as of this point there was
22 a relative lack of substantive research into the mechanisms
23 by which melatonin receptor agonists effect sleep?

24 Is that a statement you would agree with?

25 A. Yes, I think that's a fair statement.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And would you agree that the development of melatonin
2 agonists and the growth in research surrounding their
3 actions raises -- raised at that time -- some challenging
4 questions?

5 A. Yes.

6 Q. And if we go --

7 MR. GROOMBRIDGE: Let's go to Page 3, please.

8 Mr. Weir, let's enlarge Figure 1.

9 BY MR. GROOMBRIDGE:

10 Q. And here we see the structures of four molecules,
11 right?

12 A. Yes.

13 Q. And there's melatonin itself in the upper left,
14 correct?

15 A. Correct.

16 Q. And tasimelteon in the upper right?

17 A. Correct.

18 Q. And then there are two other manmade, engineered,
19 melatonin agonists, correct?

20 A. Yes.

21 Q. And one of those is something called agomelatine?

22 A. Yes.

23 Q. And the other one is something called ramelteon,
24 right?

25 A. Yes.

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1 Q. And along with tasimelteon, these were drugs,
2 engineered molecules, that were intended for use in
3 circadian rhythm applications, correct?

4 A. Circadian rhythm applications but also in the
5 treatment of depression in the case of agomelatine.

6 Q. Is that because there is a relationship or at least
7 some correlation between circadian rhythm disorders and
8 depression?

9 A. Well, agomelatine is a little bit more complicated in
10 that the sense is that it's both a melatonin agonist, but
11 has like a serotonin uptake inhibition as well. So these
12 are the SSRIs we think of as common antidepressants.

13 So I think the short answer to your question is,
14 yes, there is certainly a connection that I have published
15 on the connection between circadian rhythms and mood
16 disorders. But in the case of agomelatine specifically,
17 there's more to it than just that.

18 Q. And we can agree that neither agomelatine nor
19 ramelteon has ever been demonstrated to be capable of
20 achieving entrainment in Non-24 sufferers? Is that fair?

21 A. That's correct.

22 Q. Now, as this article reports, ramelteon is capable of
23 phase shifting, is it not?

24 A. It is.

25 Q. And is agomelatine capable of entrainment?

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1 A. I'm unaware of any studies showing that it can cause
2 entrainment.

3 Q. Fair enough. Let's turn to the next page, Page 4,
4 and just look at what the folks in the paper said about
5 that.

6 MR. GROOMBRIDGE: Let's enlarge the paragraph
7 under the heading "Agomelatine's Chronobiotic Properties."

8 BY MR. GROOMBRIDGE:

9 Q. And you see there, Doctor, your point is well taken.
10 It says: In preclinical studies, agomelatine was shown to
11 entrain the rhythm of running activities in rats, fair?

12 A. Fair.

13 Q. But it's never been shown to be capable of entraining
14 human beings; is that right?

15 A. Yes, that's correct.

16 Q. Let's just look.

17 MR. GROOMBRIDGE: Take that down and let's go to
18 Page 5, please.

19 And let's look at the -- Table 1 that appears in
20 the lower part of the page.

21 BY MR. GROOMBRIDGE:

22 Q. And Doctor, is this a kind of summary of what was
23 known in the art as of 2010 about these engineered molecules
24 that were intended to be melatonin receptor agonists?

25 A. Yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. And so we see, for example, that ramelteon in rats
2 could hasten re-entrainment of rats; is that right?

3 A. Yes.

4 Q. And the various results reported either rats or
5 humans for the various molecules in this category, right?

6 A. Correct.

7 Q. And while it mentions entrainment or re-entrainment
8 for ramelteon and agomelatine, it does not mention
9 entrainment for tasimelteon; fair?

10 A. Yes, it only mentions the 2- to 3-hour phase advance
11 with tasimelteon.

12 Q. And what it's referring to there is the work that was
13 published in what we've been calling the Rajaratnam paper,
14 right?

15 A. Yes, The Lancet paper.

16 Q. And, again, that was one of the things that you
17 talked about in your direct examination, was it not?

18 A. Correct.

19 Q. And the -- and maybe now is a convenient time to go
20 to that. So if we skip forward in the book, one, two,
21 three, four tabs, we'll come to PTX-816, The Lancet
22 Rajaratnam paper.

23 A. Yes.

24 MR. GROOMBRIDGE: Mr. Weir, that's in evidence,
25 so please put that up.

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1 BY MR. GROOMBRIDGE:

2 Q. Again, what we have here is the cover page of the
3 particular edition of The Lancet, in which this was
4 published in 2009, correct?

5 A. Correct.

6 Q. And The Lancet would -- is a well-known medical
7 journal published in England, correct?

8 A. Correct.

9 Q. And each edition, like many journals, contains
10 various learned articles, correct?

11 A. Yes.

12 Q. And each edition, they pick out one they think is
13 specifically significant to refer to on the cover; fair?

14 A. Yes.

15 Q. And in this instance, they decided, the editors, that
16 the Rajaratnam article was the one they were going to put on
17 the cover, right?

18 A. Yes.

19 Q. And they said: Football teams and many others will
20 welcome the effects of the melatonin agonist tasimelteon on
21 transient insomnia, right?

22 A. Yes.

23 Q. And the reason that football teams, in English soccer
24 team --

25 A. Yes.

CROSS-EXAMINATION - JONATHAN EMENS

1 Q. The reason they're talking about football teams is
2 because this is relating to jet lag and this is the sports
3 players who spend a lot of time frequently moving around on
4 planes, right?

5 A. Yes.

6 Q. And if we look at the actual paper itself, you refer
7 to something in this paper on your direct examination, I
8 think. And so let's go to page 7.

9 A. Yes, I'm there.

10 Q. And I'd like to start with the paragraph that ends on
11 the bottom of page 7 and goes on two lines of page 8.

12 MR. GROOMBRIDGE: Mr. Weir, let's see --

13 BY MR. GROOMBRIDGE:

14 Q. This is talking about the doses that the
15 Rajaratnam -- the paper, the researchers in the Rajaratnam
16 paper investigated, correct?

17 A. That's correct.

18 Q. And they were looking at the use of tasimelteon to
19 treat transient insomnia, such as jet lag, correct?

20 A. Yes.

21 Q. And they tested four dosage levels, correct?

22 A. Correct.

23 Q. And those were 10 milligrams, 20 milligrams,
24 50 milligrams and 100 milligrams, correct?

25 A. Correct.

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1 Q. And in this -- reporting their results they talk
2 about DLMO 25 percent, correct?

3 A. Correct.

4 Q. And that's what you mentioned DLMO, correct?

5 A. Yes.

6 Q. And that's an acronym here for dim light melatonin
7 onset?

8 A. Yes.

9 Q. And what that means, perhaps I'll get this
10 oversimplified, but there's a point when about maybe 1 to
11 2 hours before sleepiness when the body starts to produce
12 melatonin endogenously, correct?

13 A. I would be just slightly more precise. I would say
14 we start to make melatonin endogenously a few hours before
15 lights out, which, in our case, is typically associated with
16 bedtime. But it may seem like I'm splitting hairs, but I'm
17 not. It's actually an important point. It's the timing of
18 the clock relative to the main time -- for us sighted people
19 it is light.

20 Q. Right. By all means, you're not splitting hairs.

21 During the daytime the pineal gland in the brain
22 is not secreting melatonin, fair?

23 A. Yes.

24 Q. And there comes a point triggered by what is
25 abbreviated here as dim light, which it begins to secrete

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1 melatonin; fair?

2 A. Well, the dim and dim light melatonin onset refers to
3 the samples are collected in dim light because light will
4 suppress your melatonin levels. It'll hide your body's own
5 production. I like to think of that onset of melatonin a
6 little bit as kind of the beginning of your biological
7 night. It's a great way of think of it in lay terms. It's
8 kind of a marker of what time your body thinks it is, when
9 it thinks the beginning of the biological night is starting.

10 Q. And the level of endogenous melatonin is going to
11 climb like that --

12 A. Yes.

13 Q. -- during the nighttime and then it's going to start
14 to ebb away, and when it gets low enough, our body will say,
15 no, I should wake up, right?

16 A. So, again, at the risk of splitting hairs, it'll go
17 up and, like you said, it will stay up across the night and
18 then it will be decline. I don't know if I would infer
19 causality necessarily from when the melatonin levels go down
20 that causes me to wake up, however.

21 Again, I like to think of melatonin a little bit
22 slightly less as a sleep hormone and more as a marker of
23 what time it is in your body.

24 Q. And it's sometimes been referred to as the hormone of
25 darkness, correct?

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1 A. Yes, exactly.

2 Q. So if there's circulating endogenous melatonin in
3 your body, broadly speaking, during the hours of darkness?

4 A. During the hours that your body thinks are the
5 biological night.

6 Q. Again, fair enough.

7 A. Yes, which, again, for us is typically the hours of
8 when it's dark.

9 Q. And --

10 A. And we don't produce it during the hours when it is
11 light. And that is entrainment. We're producing our
12 melatonin at the same time roughly from day-to-day, both the
13 onset and when our levels are elevated.

14 Q. And that's the synchronization with the external
15 light and dark day is that because the brain has been reset
16 or cued by light, it's keeping that release of endogenous
17 melatonin synchronized with nighttime, correct?

18 A. Yes, at the approximate time each day. We have this
19 tendency to drift a little bit later because most of us our
20 day length is longer than 24 hours. We get a little bit of
21 evening light exposure. That's also going to shift us a
22 little bit later.

23 But we also get some morning light exposure that
24 shifts us earlier and that result is that we, basically,
25 most of us, stay roughly at the same place day to day. And

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1 that's entrainment.

2 Q. That's what it means to be entrained, correct?

3 A. Exactly, yes.

4 Q. So here looking back at the Rajaratnam paper, these
5 researchers having tested 10 milligrams, 20 milligrams,
6 50 milligrams and 100 milligrams, they reported that,
7 although there was a dose response relation, only
8 tasimelteon shifted DLMO 25 percent significantly earlier
9 than did placebo, correct?

10 A. Correct.

11 Q. And this is measuring phase shifting, if you will,
12 right?

13 A. Exactly, a resetting of the 24-hour biological clock.

14 Q. Mr. Stone reminds me that I skipped a number.

15 But what they are reporting here is that, of the
16 four doses they looked at, the only one that had a
17 statistically significant phase shifting effect was
18 100 milligrams, correct?

19 A. Yes.

20 Q. And I'd like to look at the --

21 MR. GROOMBRIDGE: You can take that down,
22 Mr. Weir, and let's put up the figure. In particular, the
23 part -- the bar chart in figure two, just the bar chart that
24 appears immediately above the text we're looking at.

25 BY MR. GROOMBRIDGE:

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1 Q. And you mentioned this in your direct examination,
2 did you not?

3 A. I did.

4 Q. And in your direct -- I don't think you had the
5 figure up, but you talked about a green bar here, right?

6 A. Yes.

7 Q. And that's tasimelteon 20 milligrams?

8 A. Yes.

9 Q. And you talked about how much that was able to -- in
10 these results, to effect phase shifting, right?

11 A. Yes.

12 Q. Now, we can agree that that's approximately 1 hour,
13 correct?

14 A. Yes, I think it's slightly more than one hour, but,
15 yes.

16 Q. But in this one the placebo shifted -- that achieved
17 a phase shift of 0.5 hours, correct?

18 A. Yes.

19 Q. In the text we just looked at, what the authors are
20 telling us is that there's no statistically significant
21 difference between the white bar, the blue bar, the green
22 bar, and the yellow bar, correct?

23 A. Yes.

24 Q. The only one that has statistically significant
25 effect is the red bar for 100 milligrams, right?

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1 A. Yes.

2 MR. GROOMBRIDGE: Thank you. We can take that
3 down.

4 Let me go back, if we would, let's go back one
5 tab in the book. And I apologize for jumping around, but we
6 should find there DTX-16, which is in evidence.

7 BY MR. GROOMBRIDGE:

8 Q. And this is the Hardeland paper, which is one of the
9 references in your obviousness combination.

10 A. Yes.

11 Q. And this, too, is a review article, is it not?

12 A. It is.

13 Q. Would you --

14 MR. GROOMBRIDGE: And we can put the
15 introductory information up on the screen, if you will,
16 Mr. Weir.

17 BY MR. GROOMBRIDGE:

18 Q. And what is going on here is Dr. -- or Mr. Hardeland
19 is collecting up the information that's available about
20 tasimelteon as of the date of this, which is 2009; is that
21 fair?

22 A. Yes.

23 Q. And would you agree there's no mention of Non-24 in
24 the Hardeland paper?

25 A. It does not specifically address Non-24.

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1 Q. Okay. And if we go to Page 7, DTX-16.7, I'd like to
2 look at some of the -- some of the statements here that you
3 culled out in your direct examination.

4 MR. GROOMBRIDGE: And let's enlarge in text on
5 the left at the bottom, please.

6 BY MR. GROOMBRIDGE:

7 Q. And in your slides you, I think, culled this out,
8 correct?

9 A. Yes.

10 Q. I think it was Slide 93.

11 A. Yes.

12 Q. And you said: The most effective doses for
13 tasimelteon were in the range of 20 to 50 milligrams per
14 day.

15 Correct?

16 A. Correct.

17 Q. And then -- and what's going on in this section of
18 the article is that Dr. Hardeland is talking about doses for
19 the various engineered molecules that were available in
20 development as melatonin receptor agonists, correct?

21 A. Correct.

22 Q. And so, for example, he says something called
23 Circadin is 2 milligrams per day.

24 A. Yes.

25 Q. And Circadin is an extended release form of

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1 melatonin, right?

2 A. It is.

3 Q. So that some people had felt that one of the
4 limitations of melatonin itself is that it has a short
5 half-life in the body; fair?

6 A. Fair, yes.

7 Q. Once you take it, it does whatever it's going to do
8 and then it's metabolized or cleared out of the body
9 quickly, right?

10 A. Yes.

11 Q. And there was a hypothesis that if you could make an
12 extended release version of it, it might have some
13 beneficial effect, right?

14 A. Yes.

15 Q. And that was Circadin.

16 A. Yes.

17 Q. And while we're on the point, the -- at the top of
18 the next page it says for ramelteon the recommended dose is
19 8 milligrams, correct?

20 A. Yes.

21 Q. And now just looking, the 20 to 50 milligrams, that
22 is for -- not for phase shifting, correct?

23 A. Yeah. I think they are talking there about kind of
24 the direct soporific effects.

25 Q. And if we take that down and go back and look at some

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1 of the texts just above it, under the heading Current
2 Opinion, what they say there is that: Tasimelteon
3 substantially shortened sleep onset latency, LNA and LPS,
4 especially at doses of 20 to 50 milligrams per day.

5 Do you see that?

6 A. I do.

7 Q. But then they go on when they talk about phase
8 shifting, they say it rapidly phase shifted the circadian
9 system at 100 milligrams per day.

10 Do you see that?

11 A. And it goes on to say: And presumably at smaller
12 amounts as well.

13 Q. Although these lower doses have not been tested,
14 correct?

15 A. Yeah, correct.

16 Q. And so what Dr. Hardeland is saying is that for phase
17 shifting, there's evidence to suggest that 100 milligrams
18 works; presumably lower ones would, but we have no evidence
19 of that. Fair?

20 A. No, I would disagree with that.

21 Q. You think he's a little more affirmative in -- that
22 the idea that lower doses might work?

23 A. I think that -- no, what I was disagreeing with, I
24 think, specifically is the idea that we have -- I think you
25 said there was no -- he's saying that there's no evidence

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1 that lower doses would work and I think we do have some
2 evidence to suggest that lower doses would work.

3 Q. Let's move on and try to come to wrap things up here.

4 Let's move on in the book to DTX-41, which is
5 the Non-24 application you mentioned, I think?

6 A. Yes.

7 Q. And this is also one of the items that you rely on in
8 your obviousness combinations; correct?

9 A. Yes, indeed.

10 Q. And would you agree with me there was likewise no
11 mention of Non-24 in this patent application?

12 A. Yes. Not specifically, yes.

13 Q. And would you agree with me that the -- that this
14 article also says that -- not article, patent application,
15 says that a 100-milligram dose of tasimelteon is considered
16 the lowest effective dose for phase shifting?

17 A. Well, they talk about administering 10 to
18 100 milligrams. They actually give a dose range. I'm
19 specifically looking at the Summary Invention on DTX-41.3.

20 Q. Let's turn, if we could, to page 18 of this exhibit.

21 MR. GROOMBRIDGE: And let's put up there the
22 paragraph that's numbered 11.1.2.1.

23 I'm sorry, Page 19. Page 19 of the exhibit,
24 Mr. Weir. And let's put up this paragraph here.

25 BY MR. GROOMBRIDGE:

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1 Q. And here, they're talking again about DLMO
2 25 percent, correct?

3 A. Yes.

4 Q. And that's phase shifting, correct?

5 A. Specifically it's phase, not phase shifting. DLMO
6 refers to the actual phrase.

7 Q. Correct.

8 And they then go on to say that -- the MA-1
9 means tasimelteon here, correct?

10 A. Correct.

11 Q. So they say: The tasimelteon 100-milligram dose is
12 considered the lowest effective dose for DLMO shift since it
13 was the first dose with a statistically significant P-value
14 in the ANOVA with contrasts.

15 Correct?

16 A. Yes, correct.

17 Q. Now, let's turn to the next item in the book, and we
18 should find DTX-20, also in evidence, which is the Lankford
19 paper.

20 Do you have that?

21 A. Yes. I am there.

22 Q. This is another one of the references that you rely
23 on in your obviousness combinations, correct?

24 A. Yes.

25 Q. And the -- and there's no mention of entraining in

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1 this Lankford paper, is there?

2 A. Yes, I think that's fair. I mean, it talks about the
3 ongoing Phase 3 trials, as I talked about, but I don't
4 know -- I don't think -- I think you're correct. I don't
5 think the word "entraining" is mentioned.

6 Q. And it talks about the fact that the trial is going
7 on, correct?

8 A. Exactly, yes.

9 Q. And Lankford was someone who was associated with
10 Vanda, correct?

11 A. Yes, apparently.

12 Q. And just while we have this, can you confirm for me
13 that, according to the document, it was published in May of
14 2011?

15 A. Yes.

16 Q. And the -- now, you talked about -- when you're
17 talking about reasonable expectation of success, you said
18 that, I think, the fact that a Phase 3 trial was going on
19 indicated to you that there must be a reasonable expectation
20 of success.

21 Is that a fair statement?

22 A. Yes, yes.

23 Q. Okay. And is it your view that the mere fact that
24 someone is willing to go to the trouble of doing a Phase 3
25 trial means that there must be a reasonable expectation of

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1 **success?**

2 A. Oh, I don't know if I would go so far to say there
3 must be a reasonable expectation of success, but I think it
4 would be an element, you know, that I would combine with
5 other things to decide whether a person of ordinary skill in
6 the art would have a reasonable expectation of success.

7 So I would be combining different pieces of the
8 prior art, I think, including things like Lankford, to kind
9 of come to kind of a more gestalt opinion as to whether a
10 POSA would think there would be reasonable expectations of
11 success.

12 Q. So the mere fact of a clinical trial is not by itself
13 enough to have a reasonable expectation of success in your
14 opinion.

15 A. Probably not in isolation, no.

16 Q. And the -- now, in your slides, did you cull out
17 information about time of administration of tasimelteon?

18 A. Yes.

19 Q. Now, was that time of administration with reference
20 to something other than the then-ongoing clinical trial in
21 Non-24?

22 A. Yes.

23 Q. And the times that you talked about were for earlier
24 trials that had been done in -- one in healthy volunteers,
25 one in transient insomnia patients, and one in chronic -- or

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1 primary insomnia patients, correct?

2 A. Correct.

3 Q. And Lankford says nothing about the time of
4 administration that was to be employed in the then-ongoing
5 SET trial, fair?

6 A. That is fair.

7 Q. Now, let's move on in the binder to the next item,
8 which is --

9 THE COURT: What was that exhibit you just put
10 up?

11 MR. GROOMBRIDGE: Oh, I'm sorry. It's DTX-20,
12 Your Honor, and it's already in evidence.

13 THE COURT: Okay.

14 BY MR. GROOMBRIDGE:

15 Q. Let's move to the next item in the book, which I
16 think will be our friend DTX-419, our clinical trials
17 document.

18 A. Yes, I'm there.

19 Q. And the -- is there anything in this, in the text of
20 this document, that refers to a daily sleep period of
21 approximately 7 to 9 hours?

22 A. No.

23 Q. Now, let's go on two more items in the tab here, and
24 we should find JTX-003 which is the '829 patent in this
25 lawsuit.

CROSS-EXAMINATION - JONATHAN EMENS

1 Do you have that, Doctor?

2 A. Yes, sorry, I'm there.

3 Q. And this is the so-called DDI patent that relates to
4 inhibitors of the enzyme CYP1A2. Fair?

5 A. Fair.

6 Q. And let's go to Page 10, please. Look at the figures
7 there.

8 Looking at Figure 5, does that show a map of the
9 metabolic pathways by which tasimelteon is broken down in
10 the body?

11 A. Yes.

12 Q. Would you agree with me that this was not publically
13 known as of January 2012?

14 MR. MILLIKEN: Your Honor, I object as outside
15 the scope of the direct because he didn't testify about the
16 drug-drug interaction issues specifically.

17 We're going to rely on Dr. Greenblatt's opinion
18 for that.

19 THE COURT: Okay.

20 MR. GROOMBRIDGE: Your Honor, he testified to an
21 opinion that this patent was invalid. And in our view, that
22 would make it fair to explore what's missing from the prior
23 art.

24 THE COURT: I'm going to overrule the objection.

25 BY MR. GROOMBRIDGE:

REDIRECT EXAMINATION - JONATHAN EMENS

1 Q. Doctor, would you agree with me that the information
2 that's shown in Figure 5 of the '829 patent was not known in
3 the prior art to the '829 patent?

4 A. I don't know.

5 Q. One last question. Would you agree with me that
6 melatonin, it was known that melatonin was almost
7 exclusively -- almost exclusively metabolized by CYP1A2?

8 A. Yes, that's correct.

9 MR. GROOMBRIDGE: That completes my questions.

10 THE COURT: Any redirect?

11 MR. MILLIKEN: I have just briefly, Your Honor.

12 Mr. Brooks, could we pull up DTX-41,
13 specifically at page 23.

14 And, actually, could we go one page further. I
15 apologize.

16 And then could we zoom in on that final bullet
17 point.

18 REDIRECT EXAMINATION

19 BY MR. MILLIKEN:

20 Q. Dr. Emens, do you recall testifying in your direct
21 examination about this line from the '244 Publication
22 stating that an oral dose of about 20 to about 50 milligrams
23 tasimelteon is effective in treating sleep disorders?

24 A. Correct.

25 Q. And then do you recall further talking about in your

REDIRECT EXAMINATION - JONATHAN EMENS

1 direct how the '244 Publication claims methods of treating
2 circadian rhythm sleep disorders with, among others, the
3 other doses 20 milligrams?

4 A. Yes, I do.

5 Q. Based on those disclosures, would a person of
6 ordinary skill in the art as of January 2012 have had
7 concerns about a deleterious spill over effect with a dose
8 of 20 milligrams tasimelteon?

9 A. No.

10 Q. Could you explain why that is?

11 A. Yeah. I mean, if you look at, say, the Rajaratnam
12 paper, for example, 20 milligrams caused a phase shift. So
13 if 20 milligrams causes spill over, whatever spill over it
14 caused wasn't enough to negate the phase shift that it
15 caused.

16 In other words, spill over is an explanation you
17 make afterwards to explain the magnitude of the phase shift
18 you got. So we would have known that 20 milligrams of
19 tasimelteon could cause a phase shift and maybe there is
20 spill over and -- but, again, that has nothing to
21 necessarily do with the demonstrated magnitude of the phase
22 shift that we actually see.

23 MR. MILLIKEN: And could we now go back,
24 Mr. Brooks, to, I believe it may be DTX-41.19.

25 Yes. And then could we blow up 11.1.2.1.

REDIRECT EXAMINATION - JONATHAN EMENS

1 BY MR. MILLIKEN:

2 Q. And Dr. Emens, do you recall Mr. Groombridge pointing
3 you to this paragraph when he was asking you questions?

4 A. Yes.

5 Q. And he pointed you specifically to this line about
6 the 100-milligram dose being considered the lowest effective
7 dose for DLMO shift?

8 A. Yes.

9 Q. And is that based on the data from the Rajaratnam
10 paper we have been discussing?

11 A. It is.

12 MR. MILLIKEN: Could we pull up PTX-816, please.

13 And specifically go to Page 7 and zoom in on
14 that bar chart on the right-hand side that we were looking
15 at earlier.

16 BY MR. MILLIKEN:

17 Q. And I believe you agreed in your conversation with
18 Mr. Groombridge that 100 milligrams tasimelteon was the only
19 dose that showed a statistically significant phase shift
20 versus placebo; is that right?

21 A. Yes.

22 Q. Now, the desire -- the --

23 MR. MILLIKEN: Let's actually -- instead of me
24 trying to ask this question, let's go back, please, to
25 Page 2 of this document, Mr. Brooks, and look at the Methods

REDIRECT EXAMINATION - JONATHAN EMENS

1 section.

2 BY MR. MILLIKEN:

3 Q. And you see there it says: In a Phase 3 study, 411
4 healthy individuals from 19 US sites --

5 A. Yes.

6 Q. -- who had transient insomnia induced in a sleep
7 clinic by a five-hour advance of the sleep-wake schedule?

8 A. Yes.

9 Q. And so what does that language about the five-hour
10 advance, what does that tell you about Rajarantnam's
11 results?

12 A. So for both the Phase 2 and the Phase 3 trials in
13 Rajarantnam, they advance sleep time dramatically, a full
14 five hours. Because as we discussed before, that's a nice
15 model for something like jet lag from New York to London.

16 So that's a really big phase shifting. I don't
17 need to shift a full five hours to treat, say, something
18 like Non-24. At the most, I'm only going to need an hour
19 phase shift which the 20-milligram dose gave me.

20 And, again, I would say I'm not looking, as I
21 was saying earlier, at these in isolation. I know from
22 Rajarantnam, hey, I can get a 20-milligram phase shift, and
23 I know from clinical trials that that's actually what they
24 chose in their clinical trial of Non-24.

25 And a person of ordinary skill would have had

1 access to all of that.

2 Q. Thank you, Dr. Emens.

3 Finally, did anything Mr. Groombridge asked you
4 on cross-examination cause you to change any of your
5 opinions in this case?

6 A. No, definitely not.

7 MR. MILLIKEN: Thank you, Your Honor.

8 Nothing further.

9 THE COURT: All right. I have two questions.

10 So, Dr. Emens, did they introduce your CV? Did
11 they ask to put your CV into evidence?

12 THE WITNESS: No, we just put some stuff on the
13 slide.

14 THE COURT: So you met Dr. Czeisler in medical
15 school; is that right?

16 THE WITNESS: No, I met him in between my
17 undergraduate and my medical school. And then I also
18 briefly worked in his lab during medical school actually.

19 THE COURT: All right. And then you went out to
20 Oregon.

21 THE WITNESS: Correct.

22 THE COURT: And did you go there under tutelage
23 of Dr. Sacks?

24 THE WITNESS: So Dr. Sack --

25 THE COURT: Or Sack, sorry.

1 THE WITNESS: That's okay. He did train me in
2 sleep medicine and I also worked with him and Alfred Lewy in
3 their joint laboratory as well near the end of my residency.

4 THE COURT: Did you pick your residency based on
5 your interest in sleep issues?

6 THE WITNESS: Yeah, partially. I mean, I knew
7 Al Lewy and Bob Sack were doing work similar to what I was
8 interested in, I liked the program, but that was definitely
9 a piece of it.

10 THE COURT: What do you call the doctors that
11 operate in that field? Like when you go to a conference,
12 what's the -- or when you're at a cocktail party and
13 somebody says, what do you do, what do you say you
14 specialize in?

15 THE WITNESS: Well, I'll say I specialize in
16 sleep medicine. That's the clinical part of what I do. So
17 I treat patients. But I'd also consider myself a researcher
18 in circadian physiology. So I kind of wear two different
19 hats.

20 THE COURT: All right. So sleep medicine, how
21 big is that field?

22 THE WITNESS: Sleep medicine is fairly big. I
23 mean, I don't know -- it's gotten much bigger than it was,
24 say, 30 years ago.

25 THE COURT: Like, out of how many sleep centers

1 that you would say are in the country, you know, that
2 universities or centers that have prestigious sleep centers;
3 what do you think the number is?

4 THE WITNESS: I would say any major academic
5 institution is going to have a sleep clinic, and you'll find
6 sleep clinics -- free-standing sleep clinics all over this
7 country. So there's many sleep providers all over this
8 country.

9 THE COURT: All right. Dr. Sack, is that a
10 notable name in the field?

11 THE WITNESS: Yes. I mean, he's published
12 multiple times in the New England Journal of Medicine on
13 sleep-related issues. Circadian sleep-related issues
14 specifically.

15 THE COURT: Is he still alive?

16 THE WITNESS: He is.

17 THE COURT: Have you ever testified as an
18 expert?

19 THE WITNESS: No, never.

20 THE COURT: How did you get to be retained here?
21 And I don't mean -- I don't want your private discussions
22 with counsel, but do you -- and maybe you don't know. Were
23 you just called out of the blue or --

24 THE WITNESS: Yeah, they called me up, yes.

25 THE COURT: What's the definition of sleep?

1 THE WITNESS: That's a great question.

2 So sleep is a reversible state of decreased
3 responsivity to environmental stimuli, right? So you would
4 distinguish that from, say, coma.

5 So in a coma I have a decreased response to
6 environmental stimuli but it's not a reversible state.

7 THE COURT: So you're giving the definition of
8 sleep.

9 So go ahead, say it again.

10 THE WITNESS: Yeah. So it is a reversible state
11 of decreased response to environmental stimuli. So you're
12 unconscious, but I'm distinguishing it from a state like a
13 coma that is an irreversible state of decreased response to
14 environmental stimuli.

15 THE COURT: All right. And then the definition
16 of being awake?

17 THE WITNESS: Well, that I would say, just in
18 terms of being the opposite, that would be consciousness, my
19 ability to interact with my environment and respond to
20 environmental stimuli.

21 THE COURT: Are they binary? So in other words,
22 like, I either have COVID or I don't have COVID. Am I
23 either asleep or I'm not asleep? I mean, how do doctors
24 think of it?

25 THE WITNESS: Oh, so this is an even better

1 question.

2 So they are not totally binary. So, for
3 example, there's some sensor reprocessing that's happening
4 during sleep, and there's this phenomenon of, at least shown
5 in the animals, of local sleep, where you could do a
6 high-density EEG. So I'm looking at the entire brain, and I
7 can look at your brain waves and on that basis determine if
8 you're awake or asleep. And you might see one area of the
9 brain looking like it's asleep while the rest of the brain
10 looks like it's awake.

11 So I think to call it totally binary is hard to
12 do.

13 And if you'll indulge me, at the extreme, if you
14 look at marine mammals, so dolphins breath air and yet they
15 live in the ocean. And they sleep just like we do, yet the
16 ocean is not full of dead dolphins. And so what they've
17 evolved is this idea of biphasic sleep. So there's two
18 hemispheres of their brain. One hemisphere might be awake
19 while the other is asleep, and then they trade off.

20 So that would be an extreme version of it, not
21 really being that binary that you're asking about.

22 THE COURT: Now there's been a slew of articles
23 introduced in this trial that refer to sleeping.

24 THE WITNESS: Yes.

25 THE COURT: All right. So would an artisan of

1 ordinary skill read "sleeping" to mean somebody who is in a
2 state of unconsciousness?

3 THE WITNESS: Yes.

4 THE COURT: Or is it not binary and it's
5 something they're half asleep, to use a Joe Six-Pack term?
6 Or, you know, what would an artisan of ordinary skill
7 understand if he or she were in a conversation about someone
8 who was asleep?

9 THE WITNESS: They would assume that they were
10 asleep, meaning they are unconscious, but, again, it's a
11 reversible state. That's what they would understand it.

12 And the prior art really has two main ways of
13 measuring that. Many of the prior art will just ask people.
14 So Dr. Polymeropoulos was talking about on Monday these were
15 sleep diaries. Remember he talked about they would call in.
16 They would just tell you whether they were awake or asleep.

17 Some of the studies, like Bob Sack's study in
18 the New England Journal. What Bob did is he measured brain
19 waves, eye movements, muscle tone to more objectively
20 measure sleep.

21 THE COURT: So if I'm drowsy, am I asleep?

22 THE WITNESS: You may have momentary -- if
23 you're drowsy, because of the nature of sleep and the
24 amnestic properties just before you fall asleep, you might
25 fall asleep and not even know it.

1 I observed at least two individuals asleep in
2 the courtroom on Monday. And they will remain unnamed,
3 but -- and they might not even have known that they were
4 asleep. You know, that head-bobbing effect, right, where
5 measuring brain waves they might look like they've fallen
6 asleep, and as they are falling, they have that reflex to
7 awaken themselves.

8 THE COURT: Okay. But that means that they were
9 drowsy, but within that drowsiness they had a period, it
10 might have been instantaneous, but of sleep?

11 THE WITNESS: What we would call sleep.

12 THE COURT: What an artisan would call sleep?

13 THE WITNESS: What an artisan would call sleep.

14 THE COURT: Now, if I am sleepy, am I asleep?
15 Or would an artisan treat sleepy along the lines of being
16 drowsy?

17 THE WITNESS: That's being drowsy. So
18 sleepiness is not sleep. And that's the kind of distinction
19 I think I try to make in my direct.

20 THE COURT: So is it possible to be mostly
21 asleep?

22 THE WITNESS: Yes, over a period of time, I
23 could have the majority of my time be sleep.

24 THE COURT: Okay. But you're dividing the time
25 between asleep and awake. It's just -- when you say "mostly

1 asleep" it sounds like you mean for the defined period, more
2 often than not, I'm asleep.

3 THE WITNESS: I'm asleep. And so there's this
4 measure called "sleep efficiency." So out of my total time
5 in bed, let's say I'm in bed 10 hours and 5 hours of it is
6 sleep. I'm unconscious and unresponsive. My sleep
7 efficiency would be 50 percent, half of my time asleep and
8 half of my time would be awake.

9 THE COURT: And you think an artisan of ordinary
10 skill would have that understanding?

11 THE WITNESS: Yes, definitely.

12 THE COURT: Okay. Thank you. You can step
13 down.

14 THE WITNESS: Thank you.

15 THE COURT: Can somebody put up DTX-20 on the
16 screen, please. They can zero in on the calendar. You see
17 that, right below, keep going down about one-third of the
18 way down. Right there.

19 I do want to note for the record that
20 Mr. Groombridge asked without objection if the witness could
21 tell when this article was published, published online on
22 May 9th of 2011 and it was not objected to. Just want it to
23 be noted.

24 And I'm not faulting Mr. Groombridge at all for
25 the objections he lodged, but I do think it's somewhat

1 ironic.

2 MR. GROOMBRIDGE: Yes, Your Honor, but in our
3 view there's a material difference between this and the
4 other one. That's why we weren't --

5 THE COURT: Well, there is and there isn't. But
6 like I said, it was not a frivolous objection by any stretch
7 and it should have been addressed pretrial. Not by your
8 side.

9 At the same time, I think the real issue is does
10 the Court -- should the Court have a comfort level, a
11 confidence level, that what it's looking at is, in fact,
12 what it is purported to be. Anyway.

13 All right, next.

14 MR. ROZENDAAL: Your Honor, we've come to a
15 pause in our case because our next witness, Dr. Greenblatt,
16 will not be available until tomorrow. And so by agreement
17 with the plaintiff, for which we are grateful, they will be
18 presenting some of their other case now.

19 THE COURT: Okay. Great, thank you very much.

20 And then we're going to try to do claim
21 construction?

22 MR. STONE: I believe so, Your Honor.

23 THE COURT: All right.

24 MR. GROOMBRIDGE: Yes, Your Honor. We have two
25 witnesses --

DIRECT EXAMINATION - STEVEN LOCKLEY

1 THE COURT: Today? And how long are they going
2 to be?

3 MR. STONE: Dr. Lockley will probably be on for
4 a half an hour. And I'm going to in a moment ask if we can
5 take a two-minute break because Dr. Lockley is responding to
6 what Dr. Emens just said. And I may be able to cut some of
7 it, given the cross.

8 THE COURT: That sounds good anyway. I think
9 the Court Reporter could use a break.

10 So let's come back, we'll start right at 3:15,
11 thanks.

12 (Recess taken.)

13 THE COURT: Mr. Stone.

14 MR. STONE: Thank you, Your Honor. Vanda, as
15 the beginning of its rebuttal case, calls Dr. Steven Lockley
16 to the stand.

17 THE COURT: All right.

18 MR. STONE: Your Honor, we took the liberty of
19 putting the binders around so we don't lose time.

20 THE COURT: Thank you.

21 STEVEN LOCKLEY, having been called was affirmed
22 and testified as follows:

23 DIRECT EXAMINATION

24 BY MR. STONE:

25 Q. Good afternoon, Dr. Lockley. Would you please

DIRECT EXAMINATION - STEVEN LOCKLEY

1 introduce yourself to the Court.

2 A. Yes. Hello. My name is Dr. Steven Lockley and I
3 work at the Brigham and Women's Hospital and Harvard Medical
4 School in Boston.

5 Q. And what do you do there?

6 A. I'm a researcher. I do research on circadian rhythms
7 and sleep.

8 Q. If you would, please, tell the Court what your
9 educational background is.

10 A. I received a bachelor's degree in biology in 1992 and
11 a PhD in biological sciences in 1997.

12 Q. Where did you do your PhD?

13 A. At the University of Surrey in the UK.

14 Q. And under whom did you study when you got your PhD?

15 A. That was Josephine Arendt.

16 Q. And for the court reporter, Dr. Arendt spells her
17 name A-R-E-N-D-T?

18 A. Correct.

19 Q. And who is Josephine Arendt?

20 A. She's a preeminent researcher especially in
21 melatonin, circadian rhythms, and was the first person to
22 give melatonin to people for a range of different circadian
23 disorders.

24 Q. What are you known for in the field?

25 A. I think several areas. One would be studying

DIRECT EXAMINATION - STEVEN LOCKLEY

1 circadian rhythms in blind people and then also looking at
2 the effects of light on the ability to shift circadian
3 rhythms.

4 Q. I think one of the things that might be common ground
5 in this case between the parties is that melatonin, the
6 hormone, has under certain circumstances been shown to
7 entrain the circadian rhythm; is that fair?

8 A. Yes.

9 Q. Who was the first person to demonstrate that
10 melatonin could entrain the circadian rhythm?

11 A. There were two papers in 2000, one that I coauthored
12 and one that Dr. Sack authored.

13 Q. Fair to say that you and Dr. Sack are among the
14 handful of people who are at the front of research in this
15 field?

16 A. Yes.

17 Q. Did you play any role in the SET and RESET studies?

18 A. Yes, I did.

19 Q. What was your role?

20 A. The Brigham and Women's Hospital was one of the sites
21 and I was the principal investigator for those trials.

22 Q. I think you said just that Brigham was one of the
23 sites. In the second you said hospital. Did you mean in
24 the set and reset studies?

25 A. Yes.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 Q. Thank you.

2 And sort of an off-the-wall question, do you do
3 work with NASA?

4 A. I do, yes.

5 Q. What do you do?

6 A. A range of things. We've done quite a few studies to
7 understand how light can reset astronauts when they go to
8 space station or travel across the planet.

9 Q. The sun rises every 90 minutes in space?

10 A. That's right, as you circle the earth, yeah.

11 Q. Were you here for Dr. Emens's testimony?

12 A. I was.

13 Q. And did you see that one of the things he described
14 was the chronology of what he and Mr. Groombridge called the
15 melatonin art.

16 A. Yes.

17 Q. Actually, it occurs to me before I go on.

18 MR. STONE: Your Honor, we've agreed that the
19 experts are qualified, but I offer Dr. Lockley as an expert
20 in circadian rhythm science and studies of the blind.

21 MR. COBLENTZ: No objection.

22 THE COURT: All right.

23 BY MR. STONE:

24 Q. Have you prepared today for us a slide of the
25 opinions that you'll be offering in response to Dr. Emens's

DIRECT EXAMINATION - STEVEN LOCKLEY

1 opinions?

2 A. Yes, I have.

3 Q. And is this PDX-8.2 a summary of the opinions you'll
4 be offering today?

5 A. Yes.

6 Q. And tell the Court what they are, please.

7 A. Today, I was going to talk about the attempts to try
8 and entrain blind patients with melatonin and
9 inconsistencies in the circadian phase shifting versus
10 entrainment responses.

11 Q. Have you prepared a slide summarizing what those
12 inconsistencies, as you use that term, are?

13 A. Yes.

14 Q. Why don't we look at 8.3, PDX 8.3.

15 And Dr. Lockley, if you would, walk the Court
16 through what it is you're talking about here.

17 A. So I'm going to cover the literature before 2000
18 which showed that melatonin couldn't, in fact, entrain the
19 clock at that time. And then talk about some of the reasons
20 why the spill over effect that we've heard a bit about and
21 the variation in the clock time of treatment and the
22 circadian time of treatment.

23 Q. And then what is the final point that you're making,
24 sir?

25 A. I'm making the point here there's really been no

DIRECT EXAMINATION - STEVEN LOCKLEY

1 systematic or large-scale trials to answer these questions.
2 We still don't really know the answers, for example, to how
3 to time or what doses to use for melatonin.

4 Q. When was the first reported attempt to entrain the
5 circadian rhythm using melatonin?

6 A. That was in 1988.

7 Q. And who was the principal author on that paper?

8 A. That was Professor Arendt.

9 Q. Were you there at the time?

10 A. No, no.

11 Q. Okay. Dr. Emens put up a chronology of melatonin.

12 Was this 1988 paper on it?

13 A. No.

14 Q. Why don't we -- I can't remember whether PTX-490 is
15 in evidence so why don't we turn to PTX-490 in your binder.

16 A. Yes, I see it.

17 Q. On the left side you see an article about hemorrhagic
18 pancreatitis?

19 A. Yes.

20 Q. We won't be talking about that.

21 A. Good.

22 Q. And on your right is an article "Synchronization of a
23 Disturbed Sleep-Wake Cycle in a Blind Man By Melatonin
24 Treatment."

25 Do you see that there?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. I do, yes.

2 Q. Is that the 1988 Arendt paper that you were referring
3 to?

4 A. It is.

5 MR. STONE: I offer PTX-490.

6 MR. COBLENTZ: No objection.

7 THE COURT: It's admitted.

8 (PTX-490 admitted into evidence.)

9 MR. STONE: And --

10 BY MR. STONE:

11 Q. Dr. Lockley, what are you describing in here?

12 A. This is a summary of that Arendt paper. This is the
13 first attempt to entrain a blind person with a 5-milligram
14 dose of melatonin given at 11:00 p.m. And while there's
15 evidence that his sleep pattern stabilized, there's no
16 evidence of entrainment. And that was measured with
17 multiple markers of entrainment, including melatonin,
18 cortisol and temperature measurements.

19 BY MR. STONE:

20 Q. That was melatonin, cortisol and temperature
21 measurements?

22 A. Yes.

23 Q. What was the dose that was given in that paper?

24 A. This was 5 milligrams.

25 Q. Now, there was testimony on Dr. Emens's examination

DIRECT EXAMINATION - STEVEN LOCKLEY

1 and then by the Court about Dr. Sack.

2 You're familiar with Dr. Sack, correct?

3 A. Yes, I am.

4 Q. Did Dr. Sack do any of the early efforts to entrain
5 patients using melatonin?

6 A. Yes, he did.

7 Q. Let me ask you to look in your binder at the exhibit
8 that is PTX-283.

9 A. Yes.

10 Q. What is that?

11 A. This is a paper from Dr. Sack and colleagues in 1991
12 with an attempt to entrain blind people with melatonin.

13 MR. STONE: I offer PTX-283.

14 MR. COBLENTZ: No objection.

15 THE COURT: It's admitted.

16 (PTX-283 admitted into evidence.)

17 MR. STONE: Thank you, Your Honor. Mr. Weir,
18 can we go to PDX 8.6.

19 BY MR. STONE:

20 Q. What do see here about the Sack 1991 paper?

21 A. This is a summary of their work. They report
22 studying six blind individuals. Gave them 5 milligrams of
23 melatonin at the time at 10:00 p.m. And they were able to
24 show a phase advance, but, again, did not show entrainment
25 of the clock in any of these individuals.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 Q. Dr. Lockley, is it true that anything that can
2 advance the phase can also entrain?

3 A. No.

4 Q. Okay. Are we going to come back to that later in
5 your testimony?

6 A. Yes, we will.

7 Q. Now, Dr. Emens told us and then you told us that
8 there were two studies in the year 2000 that were the first
9 that showed successful entrainment using melatonin; is that
10 right?

11 A. Yes.

12 Q. And I believe that your study is already in evidence
13 as JTX-147, but can you just look behind the next tab in the
14 binder and confirm that that's your study.

15 A. That is, yes.

16 Q. All right.

17 MR. STONE: Mr. Weir, can we have PDX 8.7.

18 BY MR. STONE:

19 Q. And the authors of this article are Lockley, that's
20 you, correct?

21 A. Yes.

22 Q. A doctor whose last names is Skene, S-K-E-N-E. Her
23 first name is Deborah?

24 A. Yes, that's right.

25 Q. And the last author is Josephine Arendt, your

DIRECT EXAMINATION - STEVEN LOCKLEY

1 supervisor for your PhD?

2 A. Correct.

3 MR. STONE: Your Honor, I don't know whether it
4 has come up in prior trials, the significance of first and
5 last author. I was going to ask him but if you've got that,
6 I'll move on briefly.

7 BY MR. STONE:

8 Q. What's the significance of being the first or last
9 author?

10 A. The first author is the person doing the day-to-day
11 work who has led the study, led the analysis. And the last
12 author is usually the senior author, the head of it.

13 Q. And is that why this paper is referred to as Lockley,
14 because you're the first author?

15 A. That's correct, yes.

16 Q. And what are we seeing here in PTX-8.7 summarizing
17 this article?

18 A. So, again, this is a summary of our study where we
19 give melatonin to seven totally blind men with Non-24.
20 Again, a 5 milligram melatonin dose given at 9:00 p.m. and
21 all of them at the same time.

22 And we were able to show that the melatonin
23 could entrain three of the seven subjects. It phase
24 advanced a fourth, but it did not entrain the remaining
25 three individuals.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 Q. Were you able at the time to determine why melatonin
2 entrained some people but not others?

3 A. We didn't have direct evidence from this trial
4 because we only had those one set of results. But we
5 hypothesized that we gave the melatonin at the wrong part of
6 the phase response curve. We accidentally timed it where it
7 wouldn't necessarily cause an advance. It would cause a
8 delay.

9 Q. Is it fair to assume that as a sighted person, you
10 can tell when my phase advance and phase delay curves are by
11 knowing what time it is?

12 A. No. I'd need to measure your clock. I could
13 estimate if you were sighted, by I couldn't tell precisely.

14 Q. How about a blind person? How does one determine
15 where they are in their curve?

16 A. You would have no idea. They can be anywhere in that
17 24-hour cycle. You really need to measure it to know where
18 their clock is.

19 MR. STONE: Forgive me, Your Honor, this may be
20 disjointed. I'm trying to not cover what was covered in the
21 last witness.

22 BY MR. STONE:

23 Q. One of the other references that Dr. Emens talked
24 about is a reference we have been calling Hack.

25 Is that right?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. Yes.

2 Q. Let me ask you to look at JTX-146, which is two tabs
3 or one tab forward in the binder.

4 A. Yes.

5 Q. The first author -- well, it's in evidence.

6 MR. STONE: So Mr. Weir, can we see PDX-8.9.

7 BY MR. STONE:

8 Q. The first author on the Hack paper is Lisa Hack,
9 correct?

10 A. That's right.

11 Q. Who is the second author on it?

12 A. I am.

13 Q. Tell us what we're looking at in the summary of the
14 Hack and Lockley paper.

15 A. In this study of ten totally blind with Non-24 we
16 gave a smaller dose, 0.5-milligram dose of melatonin.
17 Again, at 9:00 p.m. And we had very mixed result in this
18 study. We showed that four subjects entrained immediately,
19 two additional subjects entrained after 3 to 4 weeks of
20 treatment. One person phase advanced and the others weren't
21 able to be entrained.

22 Q. Dr. Emens referred to this in his direct examination
23 as having shown entrainment.

24 What is the significance of the fact that four
25 out of the ten people in the study, in fact, did not

DIRECT EXAMINATION - STEVEN LOCKLEY

1 entrain?

2 A. Well, we were able to show entrainment but only in
3 some individuals. And so both in this study and my previous
4 one, we didn't show entrainment in everyone, and we don't
5 really understand why.

6 Q. Did you and your colleagues offer some thoughts in
7 this paper as to what the dose effect might be?

8 A. Yes, we did.

9 MR. STONE: Why don't we go to the next slide,
10 Mr. Weir, 8.10.

11 BY MR. STONE:

12 Q. Dr. Lockley, what are we seeing here?

13 A. This is an excerpt from that paper where we say that
14 a lower dose of melatonin would be preferable to a higher
15 dose to reduce long-term side effects. You would want to
16 give a lower dose of the drug if it worked as well as a
17 higher dose.

18 Q. And do we now know that there is another reason that
19 one might want to give a lower dose of melatonin besides
20 side effects?

21 A. Yes, we do.

22 Q. And what's the reason?

23 A. That's spill over effect and spill over hypothesis.

24 Q. We're going to come to that shortly although in less
25 depth than we might have.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 MR. STONE: Can we have the next slide, please,
2 8.11.

3 BY MR. STONE:

4 Q. Dr. Lockley, are these data that appear in your Hack
5 and Lockley paper?

6 A. They are, yes.

7 Q. Why don't you walk the Court through what it is that
8 we're looking at here.

9 A. So these are data from four of the ten individuals
10 illustrating the variability and the different responses.
11 And we've seen the disorder of Non-24 is characterized by
12 this progressive delay, the shifting later of, in this case,
13 melatonin and cortisol.

14 So you can see before treatment this individual
15 was running later and later. Then when they were given
16 melatonin, you can see that they entrained. This line
17 becomes vertical. They lock on, they stay entrained until
18 they stop treatment, and then they go off again.

19 So this is an example of entrainment.

20 In this individual, we entrained after a lag,
21 and so they are nonentrained before, but they stay
22 nonentrained for several weeks until they then lock on and
23 entrain with a lag. And this happened in two people.

24 This individual had a shortened period, so they
25 were not entrained before. They stayed nonentrained, but

DIRECT EXAMINATION - STEVEN LOCKLEY

1 you can see the slope of this line is different but not
2 vertical. So they still had a nonentrained period of 24.45.
3 Then they reverted.

4 And in this individual, again, there was no
5 effect of the melatonin at all on entrainment. You can see
6 that the rhythm just keeps on going later and later and
7 later and treatment has never failed.

8 BY MR. STONE:

9 Q. Now, one of the things you told us was discussed in
10 this paper was a recommendation to consider lower doses of
11 melatonin, correct?

12 A. Yes.

13 Q. Did subsequent studies then explore lower doses in
14 using melatonin to entrain?

15 A. Yes, not in our laboratory but in Dr. Lewy's
16 laboratory.

17 Q. Why don't we go to the next slide, PDX 8.12.

18 Is this a chart that you prepared of some of the
19 papers that were looking during this period at lower
20 melatonin doses?

21 A. Yes.

22 Q. What do we see here?

23 A. So we can see a series of fairly small studies
24 showing that, first of all, three patients could entrain
25 with a 0.5-milligram dose. Then more patients with 0.5 and

DIRECT EXAMINATION - STEVEN LOCKLEY

1 one even with 0.05-milligram dose.

2 Then a series of case studies of ten individuals
3 with lots of different doses that we used, all
4 individualized in the patients, from very small doses of
5 20 micrograms up to .3 milligrams.

6 And then this series of cases of individuals
7 that we heard about earlier who could not be entrained with
8 20 milligrams, could not be entrained with 10 milligrams but
9 could be entrained with a 0.5 and later 0.3 milligram dose.

10 So there's a lot of variability in the success
11 of these doses as you get smaller.

12 Q. In all of the melatonin art that existed prior to the
13 beginning of 2012, the priority date, was there ever an
14 example of anybody being entrained using 20 milligrams of
15 melatonin?

16 A. No.

17 Q. You have mentioned a couple of times and Dr. Emens
18 talked about the spill over effect. I don't want to cover
19 the ground already covered, but I do want to start here.
20 Would you turn to JTX-123. It's in your binder.

21 A. Yes.

22 Q. Do you recognize this to be a paper that
23 Mr. Groombridge discussed with Dr. Emens during his
24 cross-examination in which the authors included Dr. Lewy and
25 Dr. Emens and Dr. Sack?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. Yes.

2 Q. I'm told Mr. Groombridge forgot to offer it into
3 evidence.

4 MR. STONE: So I offer JTX-123.

5 MR. COBLENTZ: No objection.

6 THE COURT: It's admitted.

7 (JTX-123 admitted into evidence.)

8 MR. STONE: Go to the next slide, PDX 8.15.

9 BY MR. STONE:

10 Q. Dr. Lockley, are these sections that you selected to
11 call out of the Lewy and Emens paper?

12 A. Yes.

13 Q. Tell us what we're looking at in the top box.

14 A. So this summarizes the results I just mentioned where
15 an individual could not be entrained to a 20-milligram dose
16 of melatonin, but could now be entrained to a lower dose of
17 0.5 milligrams.

18 Q. You used the articulation to "be entrained to a
19 dose."

20 Is it also sometimes said "entrained by a dose"?

21 A. Yes, there's no difference.

22 Q. Okay. So you're giving a dose of 20 milligrams, it's
23 not resulting in entrainment. You're giving a dose of a
24 half a milligram, it is resulting in entrainment?

25 A. Correct.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 Q. All right. And what is the middle box telling us?

2 A. So this shows one of the reasons that Lewy and
3 colleagues proposed why 20 milligrams did not entrain
4 because of the spill over effect. The idea that if you have
5 a higher dose of melatonin, it hangs around the body longer
6 and spills over into the wrong zone of that phase response
7 curve either reducing the advance you're trying to achieve
8 or sometimes abolishing it.

9 Q. And PRC is an abbreviation for phrase response curve?

10 A. Correct.

11 Q. Have you prepared a demonstrative exhibit for the
12 Court to just lay out simply what that looks like?

13 A. I have, yes.

14 Q. All right. And I'm pulling up PDX-8.16.

15 I want to come back to something we dealt with
16 earlier in the trial, which is the side by side presentation
17 of the same data, which I will confess seems baffling to me.

18 Could you explain why one presents it this way?

19 A. We usually double-plot the data. It's just for ease
20 of illustration so you can see the cycle go on and on.

21 So this is just the same cartoon of a phase
22 response curve plotted next to each other.

23 Q. And at any given point in the curve -- I think I have
24 a laser pointer -- if one administers melatonin in this
25 instance at 9:00 p.m., what is the -- or anywhere before

DIRECT EXAMINATION - STEVEN LOCKLEY

1 1:00 a.m., what is the effect on the curve?

2 A. That would phase advance the clock or shift the clock
3 earlier.

4 Q. And if one administers melatonin after 1:00 a.m.,
5 what effect would that have?

6 A. That would cause a delay shift or shift the clock
7 later.

8 Q. And if we look at 8.17, you've prepared something for
9 us that talks about a small discreet dose at 1:00 p.m.

10 Why don't you tell us about that.

11 A. So this is to try to help understand the spill over
12 effect.

13 And so if we were to give a small dose of
14 melatonin at about 1:00 p.m. in this example, and it lasted
15 in the circulation for only about 12 hours, shown by the
16 next slide, you would see that we would only be giving
17 melatonin coincident with this phase advance part of the
18 PRC.

19 And so giving it at this time would cause an
20 advance, and as it remained in circulation, it would still
21 continue to cause an advance because it's a lower dose and
22 would be cleared within this 12-hour example.

23 Q. And what happens if we give a larger dose?

24 We're now on PDX-8.18.

25 A. So this is an example of what would happen with a

DIRECT EXAMINATION - STEVEN LOCKLEY

1 higher dose given at the same time, but now this dose,
2 because it's higher, lasts in the circulation for longer.
3 And so we would get potentially this initial advance, but it
4 would be undone because of this spill over of the melatonin
5 into the phase delay part of the PRC which would either
6 reduce the advance achieved by giving it here, the right
7 side, or abolish it if it counteracted the advance.

8 Q. And could you sum up for the Court what your second
9 bullet on this slide explains.

10 A. Yeah. So the spill over effect explains why it's
11 important to give the proper dose of melatonin at the proper
12 time because you want to give the smaller doses to get that
13 discreet time queue so it doesn't spill over, but also give
14 it at the proper time to cause the phase advance that we
15 need for Non-24-Hour people with a clock longer than 24.

16 Q. One of the things -- I'm going to skip ahead in the
17 interest of time.

18 One of the things that Dr. Emens and
19 Mr. Groombridge discussed on cross-examination is the
20 different reports in the melatonin art about the clock time
21 of treatment, 9:00 p.m. as measured by the clock on the
22 wall, and the circadian time of treatment and what time is
23 it for that blind person when you give it.

24 A. Yes.

25 Q. Were you here for that discussion?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. I was, yes.

2 Q. Did you hear Dr. Emens to have said that only the
3 circadian time matters, the person's internal time, not the
4 clock on the wall time.

5 A. Yes, I did hear that.

6 Q. Do you agree with that?

7 A. No.

8 Q. Why not?

9 A. Because we want to also make sure we give it at a
10 time where the potential sleepiness effects of melatonin
11 don't interfere with the patient's lifestyle.

12 Q. Would you want to entrain someone to become sleepy
13 every day at 10:00 a.m.?

14 A. No, no, no.

15 Q. So is it therefore important to know what time you
16 are trying to entrain them to?

17 A. Yes. You want to give it at the right circadian time
18 to cause the shift you're trying to achieve, but also the
19 clock time that doesn't interfere with their lifestyle and
20 make them sleepy at the wrong time of day.

21 Q. And is the time of treatment one of the things that
22 varies in the melatonin art?

23 A. Yes.

24 Q. Why don't we look at -- let's look at Slide PDX-8.21.

25 Dr. Lockley, what are you representing here?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. So this is a summary of those main studies we've
2 talked about earlier, showing the variability in the timing.

3 In our studies, we gave it a fixed clock time of
4 9:00 p.m. at the correct circadian phase, or we tried to, in
5 everyone. Sack also did something similar in the earlier
6 studies, but in later studies you can see the timing changed
7 to either about an hour before bedtime, one to two hours
8 before bedtime, and at very varying sets of times in the
9 2005 period anywhere from 5:00 p.m. to 1:00 a.m.

10 Q. But by the time of the priority date in this case,
11 was it understood when exactly to give melatonin for
12 purposes of entrainment?

13 A. No, and it still isn't.

14 Q. I'm sorry, did you say it still isn't?

15 A. It still isn't, no.

16 Q. Let's talk about circadian time of treatment.

17 Just to be clear, what does that refer to?

18 A. So this is the time according to the internal
19 biological clock, the internal clock time of circadian.

20 Q. And why does that matter in terms of when one
21 administers it?

22 A. The circadian time refers -- it goes back to the
23 phase response curve. It's the PRC which describes the
24 impact of giving it at the right circadian time when we're
25 trying to advance, for example.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 Q. Now, you told us earlier -- I'm going to skip ahead,
2 forgive me -- that there were no systematic or large-scale
3 clinical trials.

4 Do you remember saying that?

5 A. Yes.

6 Q. All right. Is the fact -- withdrawn.

7 Was the fact that the melatonin art was
8 conflicting actually discussed in the melatonin art itself
9 prior to the priority date?

10 A. Yes, it was.

11 Q. If you would turn in your binder to DTX-39, this is a
12 document that was put into evidence with Dr. Emens. And
13 it's a paper by Dr. Deborah Skene, S-K-E-N-E, and
14 Dr. Arendt, your mentor.

15 Do you recognize this article?

16 A. I do, yes.

17 Q. Dr. Emens said that the article described that there
18 was, at that point in 2007, a consensus that melatonin could
19 entrain.

20 Do you recall hearing him say that?

21 A. Yes.

22 Q. Does the article talk as well about what else remains
23 to be understood?

24 A. Yes, it does.

25 Q. Why don't you tell us what we're looking at here,

DIRECT EXAMINATION - STEVEN LOCKLEY

1 please.

2 A. So here's an excerpt from that paper saying that
3 further studies are needed, first of all, to work out what
4 the minimum effective dose is because the right dose was
5 certainly not decided by then, and what the ideal dosing
6 regime may be, how to give it, is it every day, every second
7 day, and even the formulation, the type of melatonin used.

8 And then some of the reasons why people don't
9 entrain: Is that because of individual differences in the
10 internal clock time or individual differences in how they
11 process melatonin?

12 And so it certainly wasn't decided by 2007 how
13 to give melatonin and what was best.

14 Q. Has there been subsequent research into -- well,
15 withdrawn.

16 Let me ask you to look at JTX-149 in your
17 binder. It's the second-to-last document.

18 A. Yes.

19 Q. This is an article entitled: Clinical Practice
20 Guideline For the Treatment of Intrinsic Circadian Rhythm
21 Sleep-Wake Disorders, and then it has several other words in
22 the title.

23 Do you see that there?

24 A. I do.

25 Q. And this is from 2015, so it's after the priority

DIRECT EXAMINATION - STEVEN LOCKLEY

1 date, correct?

2 A. Yes.

3 Q. Dr. Emens is one of the authors of this article?

4 A. Yes.

5 MR. STONE: I offer JTX-149.

6 MR. COBLENTZ: No objection.

7 THE COURT: It's admitted.

8 (JTX-149 admitted into evidence.)

9 BY MR. STONE:

10 Q. One of the things that appears in this article is the
11 following Figure 6, and you'll see there that it's referring
12 to your Lockley paper in 2000, the Hack and Lockley paper in
13 2003, and the Sack paper from 2000.

14 Do you see that there?

15 A. I do.

16 Q. What is this article saying about those papers?

17 A. So it's summarizing the art in using melatonin to
18 entrain or to treat blind people with Non-24, and there are
19 only three studies that they could consider because the
20 associated numbers are sufficient at controlling the study,
21 and those are two of the papers from the Arendt lab, the
22 Lockley and Hack, and then the one Sack paper from 2000.

23 And they, in these recommendations, say that
24 melatonin should be strategically timed but give a range of
25 times. They talk about either 9:00 p.m. or one to two hours

DIRECT EXAMINATION - STEVEN LOCKLEY

1 before bedtime. And so there's very little prior evidence
2 to make a clinical recommendation.

3 And, again, there's still no clarity on how to
4 time melatonin or what dose to give.

5 Q. Let's look at one last document. If you could turn
6 to JTX-139, it's the last document in the binder, and it is
7 in evidence through Dr. Emens.

8 Do you recognize this to be a paper by Steven
9 Deacon and Josephine Arendt?

10 A. Yes, I do.

11 Q. And this is from 1995; is that right?

12 A. Correct.

13 Q. Have you prepared a chart talking about some of the
14 conclusions from this article?

15 A. I have, yes.

16 Q. Why don't we look at PDX-8.28.

17 This article concluded that a single dose of
18 melatonin could shift the circadian clock, correct?

19 A. That's correct.

20 Q. That's a phase advance?

21 A. That's right.

22 Q. What are you then showing us with the next table,
23 please?

24 And to be clear, this table is not something
25 excerpted from the document; you created this.

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. I created this, yes.

2 Q. All right. Please continue.

3 A. So this summarizes the results of the study. They
4 were able to find a dose response; meaning that the more
5 melatonin you gave, the bigger the phase shift achieved.
6 And so a 0.05 dose achieved about a .36-hour shift; a 5
7 milligrams dose as much as 1.43.

8 Now if I were to try and take these phase
9 shifting data to predict what would happen for entrainment
10 in a blind person, theoretically, there should be this
11 translation. Meaning I can shift by .36 hours with a 0.05
12 dose, I should be able to entrain someone within a period of
13 24.36. I should be able to shift by this much per day.

14 Q. Let me pause you there for a moment.

15 And the way you would do that is if the
16 melatonin shifts by .36 hours, you'd give it everyday, and
17 it would counteract someone whose tau is 24.36?

18 That's the theory?

19 A. That's correct. That's the theory.

20 Q. Keep going.

21 A. And so if we use a 5-milligram dose, you'd predict
22 that someone with a period as long as 25.43 could be
23 entrained by giving that 5-milligram dose every day.

24 Q. How does 25.43 as a tau relate to the actual blind
25 population?

DIRECT EXAMINATION - STEVEN LOCKLEY

1 A. There isn't anyone with a tau who has been measured
2 to be that long. I believe the longest in the literature is
3 25.1.

4 Q. Okay. So now please continue.

5 A. So these predictions don't hold, however. So you
6 can't take the phase shifting data from a single dose and
7 then know anything about whether that will entrain these
8 periods. Because 24.7 hours was recited as the longest
9 period that either the 5- or 10-milligram dose should be
10 entrained where, theoretically, it should be as long as
11 25.43.

12 The smaller dose to .5 should be limited to
13 around 24.69 but, in fact, has been shown to entrain
14 somewhat with a 24.9-hour clock.

15 And the 5-milligram dose should be able to
16 entrain every blind person, theoretically, because, as I
17 said before, no one has been shown to even have a period
18 this long.

19 Of course that's not true. In our 5-milligram
20 studies, only three out of the seven patients were
21 entrained.

22 Q. So what does one take away from the melatonin art
23 regarding the relationship between the ability of a
24 substance to phase shift and the ability of it to entrain?

25 A. You can't draw inference from phase shift to

DIRECT EXAMINATION - STEVEN LOCKLEY

1 entrainment. You need to shift to cause entrainment, but
2 the amount of shift you get with a single dose does not tell
3 you how much you need to entrain.

4 Q. Have you prepared a chart for the Court that
5 summarizes the melatonin art in terms of dosage and time of
6 administration?

7 A. I have, yes.

8 Q. I'm pulling up PDX-8.29.

9 And without going through each line, what do we
10 see here?

11 A. So this summarizes much of the work we've talked
12 about today. So summarizing the range of doses here
13 anywhere from very small doses of 0.02 milligrams all the
14 way to 20 milligrams, and the range of timings, bedtime all
15 the way down to around 5:00 p.m.

16 So there's a lot of variability in the research.

17 Q. And in the history of this melatonin art, how many
18 times -- well, how many times was 20 milligrams of melatonin
19 shown to entrain?

20 A. Never.

21 Q. And have you prepared as a last slide a summary of
22 your opinions?

23 A. I have, yes.

24 Q. Why don't you walk the Court through what that is.

25 A. So, briefly, the melatonin art provides conflicting

CROSS-EXAMINATION - STEVEN LOCKLEY

1 information as to the appropriate dose of melatonin. Doses
2 as low as 0.05 milligrams and as high as 10 milligrams have
3 been shown to entrain in some people, but .5, 5 and 10
4 sometimes fails to entrain.

5 The one person studied with 20 milligrams of
6 melatonin did not entrain. The high doses of melatonin may
7 not entrain due to the spill over effect hanging around
8 essentially too long and confusing the brain. And there's
9 lots of variability in the studies as to the appropriate
10 clock time or circadian time to either start treatment -- to
11 start treatment to initiate treatment.

12 And the study looking at the phase shifting
13 effects of a single dose cannot tell you whether melatonin
14 can entrain or what dose to use to entrain.

15 MR. STONE: I thank you for working with me to
16 shorten this, and I pass the witness, Your Honor.

17 THE COURT: All right. Cross.

18 MR. COBLENTZ: We have cross binders to pass up.

19 May I approach, Your Honor.

20 THE COURT: Yes.

21 CROSS-EXAMINATION

22 BY MR. COBLENTZ:

23 Q. Good afternoon, Dr. Lockley.

24 A. Hello.

25 Q. You do not have a medical degree; isn't that correct?

CROSS-EXAMINATION - STEVEN LOCKLEY

1 A. No. I have a PhD.

2 Q. And you have never diagnosed a patient with Non-24;
3 is that correct?

4 A. Correct.

5 Q. And you are not licensed to treat or prescribe
6 medication; is that correct?

7 A. Correct.

8 Q. And you never treated a patient in a clinical setting
9 with tasimelteon; is that correct?

10 A. Correct.

11 Q. Now, if we can go to JTX-147 in your binder.

12 MR. COBLENTZ: And Mr. Brooks, if you could pull
13 that up on the screen.

14 BY MR. COBLENTZ:

15 Q. This is a paper you discussed in your direct that you
16 authored in the year 2000; isn't that correct?

17 A. Yes.

18 Q. And if we look at the end of the abstract here on the
19 first page, over in the right-hand column, we see that this
20 paper says that: These results show for the first time that
21 daily melatonin administration can entrain free-running
22 circadian rhythms in some blind subjects assessed using
23 reliable physiological markers of the circadian rhythm.

24 Is that what that says?

25 A. Yes.

CROSS-EXAMINATION - STEVEN LOCKLEY

1 Q. And if we go to Page 5 of JTX-147, this is part of --
2 if you look at the right-hand column before the
3 acknowledgments, this is part of the discussion section of
4 the paper; is that correct?

5 A. Yes.

6 Q. And you state here: In summary, the present study
7 shows that the first demonstration of entrainment of
8 free-running blind subjects by melatonin treatment assessed
9 using reliable physiological markers of the circadian
10 system.

11 Isn't that correct?

12 A. Yes.

13 Q. Now I'd like to go to JTX-148.

14 And this is the -- a paper by Robert Sack from
15 2000; is that correct?

16 A. Yes.

17 Q. And you considered this paper as part of your
18 opinions; is that correct?

19 A. I did, yes.

20 Q. Now, if we look at the abstract here in the Methods
21 section, we see it states here that: We performed a
22 crossover study involving seven totally blind subjects who
23 had free-running circadian rhythms.

24 Do you see that?

25 A. Yes.

CROSS-EXAMINATION - STEVEN LOCKLEY

1 Q. And then it says: The subjects were given
2 10 milligrams of melatonin or placebo daily, one hour before
3 their preferred bedtime, for three to nine weeks.

4 Is that correct?

5 A. Yes.

6 Q. Now, if we go down to the Conclusion section of the
7 abstract, they state that: The administration of melatonin
8 can entrain circadian rhythms in most blind people who have
9 free-running rhythms.

10 Is that correct?

11 A. Yes, that's what it says.

12 Q. Now, I'd like to go to Page 5 of JTX-148 and
13 specifically look down at the Discussion section of the
14 paper, and it's the second sentence in the Discussion
15 section that I want to focus on.

16 And here the Sack paper says: Our results
17 indicate that phase-advancing effects of melatonin are of
18 sufficient magnitude to entrain free-running circadian
19 rhythms in most blind persons who have such rhythms.

20 Do you see that?

21 A. I do.

22 Q. Now, I'd like to -- now, this particular paper, it
23 was published in the New England Journal of Medicine; is
24 that correct?

25 A. Yes.

CROSS-EXAMINATION - STEVEN LOCKLEY

1 Q. That's a peer-reviewed publication?

2 A. That's correct.

3 Q. It is a well-respected publication?

4 A. It is.

5 Q. Now I'd like to go to JTX-146.

6 Now JTX-146, this is the Hack paper that you
7 discussed in your direct examination; is that correct?

8 A. Yes.

9 Q. And you're an author on this paper, correct?

10 A. I am.

11 Q. Now look at the abstract here, the very first
12 sentence, it says: Exogenous melatonin (0.5 to
13 10 milligrams) has been shown to entrain the free-running
14 circadian rhythms of some blind patients.

15 Is that correct?

16 A. Some blind subjects.

17 Q. I'm sorry. I think I did that in your deposition,
18 too. Let me read that again.

19 So it says: Exogenous melatonin (0.5 to
20 10 milligrams) has been shown to entrain the free-running
21 circadian rhythms of some blind subjects.

22 Did I read that correctly?

23 A. Correct.

24 Q. Now, if we go to Page 2 of JTX-146, and I want to
25 look at the second paragraph, now the first part of this

CROSS-EXAMINATION - STEVEN LOCKLEY

1 paragraph, it talks about early studies before 2000 using
2 melatonin to entrain free-running rhythms.

3 Is that correct?

4 A. Where are you referring to?

5 Q. If we look at the papers that talk about Sack 1991
6 down below, 1995, Arendt 1997, Sack and Lewy 1997?

7 A. Yes.

8 Q. Now, the next sentence after those says: In
9 contrast, several recent studies have re-examined the
10 ability of melatonin to entrain free-running rhythms in
11 totally blind people and found that entrainment could be
12 achieved following daily oral melatonin treatment with
13 5 milligrams.

14 Do you see that?

15 A. Yes.

16 Q. And there it cites that Lockley 2000 paper that we
17 just went over with; is that correct?

18 A. Yes.

19 Q. And then it says 10 milligrams, and it cites that
20 Sack 2000 paper.

21 Do you see that?

22 A. Yes.

23 Q. And then after that it has the 0.5-milligram doses,
24 and it cites the Lewy 2001 paper; is that correct?

25 A. Yes.

CROSS-EXAMINATION - STEVEN LOCKLEY

1 Q. And the Lewy -- Dr. Lewy worked with Dr. Sack; is
2 that correct?

3 A. Yes.

4 Q. Now, if we go to Page 5 of JTX-146, and we look at
5 the Discussion section, which is in the right-hand column,
6 it says here that: The present results show that
7 appropriately timed, low-dose melatonin (0.5 milligrams) can
8 entrain free-running circadian rhythms in most blind people.

9 Do you see that?

10 A. Yes.

11 Q. And then it says: This finding confirms and extends
12 a previous report of entrainment of three free-running blind
13 people with 0.5 milligrams melatonin.

14 Do you see that?

15 A. Yes.

16 Q. And that cites the Lewy 2001 paper; is that correct?

17 A. Yes.

18 Q. And that's the other lab that was working on this,
19 the Sack lab; is that correct?

20 A. Correct.

21 Q. Now I'd like to go to DTX-39. This is a paper by
22 Dr. Skene and Dr. Arendt; is that correct?

23 A. Yes, it's a review.

24 Q. And that was going to be my next question, so thank
25 you.

CROSS-EXAMINATION - STEVEN LOCKLEY

1 This is a review article; is that correct?

2 A. Yes.

3 Q. And in the abstract of this particular review
4 article, we see there's a sentence that says: Daily
5 administration.

6 Do you see where I'm at?

7 A. Yes.

8 Q. And it says: Daily administration of exogenous
9 melatonin is the current treatment of choice for this
10 so-called non-24 h sleep/wake disorder.

11 Do you see that?

12 A. Yes.

13 Q. And it says after that, it says: Melatonin has been
14 shown to correct the underlying circadian rhythm abnormality
15 as well as improve sleep and reduce daytime napping.

16 Do you see that?

17 A. Yes.

18 Q. Now, if we go to Page -- DTX-39.3. And we look at
19 the Treatment section here.

20 Let me know when you're there.

21 A. I have a DTX-39, but that's the Skene and the --

22 Q. Yes, so we're in the same reference. We're looking
23 at Page 3 of that reference.

24 A. Sorry, I was confused with the .3. Yes.

25 Q. And it says in the second paragraph there, it says:

CROSS-EXAMINATION - STEVEN LOCKLEY

1 Appropriately timed, exogenous melatonin has been shown to
2 advance or, more controversially, delay the timing of the
3 circadian clock.

4 Do you see that?

5 A. Yes.

6 Q. It says: Melatonin's phase shifting effect
7 presumably occurs by means of receptors in the SCN (not
8 MT-1, possibly MT-2) although this has yet to have been
9 definitely proven.

10 Do you see that?

11 A. Yes.

12 Q. In recent years, this phase shifting effect of
13 melatonin has been employed successfully to entrain totally
14 blind people with free-running circadian rhythms.

15 Do you see that?

16 A. Yes.

17 Q. And it cites to a 29 and a 30; is that correct?

18 A. Yes.

19 Q. And if we go to DTX-39.5, Reference 29 is that
20 Lockley 2000 paper; is that correct?

21 A. Yes.

22 Q. And then Reference 30 is the Sack 2000 paper; is that
23 correct?

24 A. Yes.

25 Q. Now, if we go to DTX-39.3, I want to go back to where

CROSS-EXAMINATION - STEVEN LOCKLEY

1 we just were in the treatment section, and there's a
2 sentence that says: In our studies. It says: In our
3 studies, entrainment by melatonin has occurred by the
4 ability of melatonin to phase advance the circadian clock.

5 Do you see that?

6 A. Yes.

7 Q. And, again, it cites to the Reference 29 and then 31.

8 Do you see that?

9 A. Yes.

10 Q. Now, if we go to DTX-39.5, you see that, again,
11 Reference 29 is the Lockley 2000 paper and Reference 31 is
12 the Hack paper; is that correct?

13 A. Yes.

14 Q. Now I'd like to go back to DTX-39.3 and look at the
15 bottom of the Treatment paragraph.

16 And you see it says: Recent research.

17 Do you see that?

18 A. Yes.

19 Q. And it says: Research has been directed at
20 determining the minimum effective dose of melatonin for
21 entrainment.

22 Do you see that?

23 A. Yes.

24 Q. And then it says: Melatonin at a daily dose of
25 0.5 milligrams has been shown to effectively entrain

CROSS-EXAMINATION - STEVEN LOCKLEY

1 free-running rhythms in blind people before.

2 Do you see that?

3 A. Yes.

4 Q. Now, I'd like to go to DTX-331.

5 Let me know when you're there.

6 A. Yes, I'm there.

7 Q. Now, this is an e-mail chain, and I'd like to focus
8 on --

9 MR. COBLENTZ: Go to DTX-331.3.

10 If we blow up the bottom e-mail.

11 So for the record, I think this was offered
12 already into evidence.

13 MR. STONE: And if it hasn't, I have no
14 objection to it.

15 THE COURT: All right.

16 BY MR. COBLENTZ:

17 Q. And this is an e-mail sent on June 1st of 2012 from a
18 Gabrielle Thibodeau to you and copying Marlene Dressman.

19 Do you see that?

20 A. Yes.

21 Q. And the subject is: Sleep 2012 posters for review.

22 Do you see that?

23 A. Yes.

24 Q. And Ms. Thibodeau asking you to review Word versions
25 of, I guess, drafts of these posters; is that correct?

REDIRECT EXAMINATION - STEVEN LOCKLEY

1 A. Well, both. The Word version and the PowerPoint
2 version, yes.

3 Q. If we go to DTX-331.2, and we see here that you
4 respond to Ms. Thibodeau on June 5th of 2012.

5 Do you see that?

6 A. Yes.

7 Q. And if we go to the third paragraph of your e-mail,
8 you state here: None of them acknowledge that melatonin can
9 entrain the circadian rhythms of blind people (Lockley, et
10 al, 2000, and Sack et al, 2000) which is what led to the
11 thinking that tasi might be effective.

12 Do you see that?

13 A. Yes.

14 Q. And you say: It's hard to shy away from that fact
15 even though I understand why.

16 Do you see that?

17 A. Yes.

18 Q. Now, Dr. Lockley, in your direct examination, you do
19 not provide any analysis of whether the asserted claims of
20 the patents-in-suit were obvious or not obvious, correct?

21 A. Correct.

22 MR. COBLENTZ: I have nothing further.

23 THE COURT: Redirect?

24 MR. STONE: Very briefly, Your Honor.

25 REDIRECT EXAMINATION

REDIRECT EXAMINATION - STEVEN LOCKLEY

1 BY MR. STONE:

2 Q. I can't leave that hanging there.

3 Could you turn to DTX-331, please?

4 A. Yes.

5 Q. This e-mail exchange between you and Ms. Thibodeau
6 and Ms. Dressman, the subject line is: Sleep 2012 posters
7 for review.

8 Right?

9 A. Yes.

10 Q. What posters were you talking about?

11 A. There are, I think, five posters that they sent me to
12 be presented at the -- the annual sleep meeting in 2012.

13 Q. And what would those posters have been reporting on?

14 A. They would have been a range of results -- I can't
15 tell from this e-mail, but they would have been different
16 aspects of the SET and RESET trials.

17 Q. But just to zoom out, since this is the first time
18 this has come up, this is about posters about the SET and
19 RESET work?

20 A. Correct.

21 Q. And you reply at 12:26 in the morning?

22 A. Yes, it looks like it.

23 Q. And you write in the first paragraph: Sorry this is
24 so late. I had a grant deadline.

25 Do you see that there?

1 A. I do, yes.

2 Q. You then provide, you know, a page and a half of
3 comments?

4 A. Yes.

5 Q. Okay. So you said: None of them acknowledge that
6 melatonin can entrain the circadian rhythms of blind people,
7 citing your paper and Sack.

8 Right?

9 A. Yes.

10 Q. Which is what leads to the thinking that tasimelteon
11 might be effective.

12 Do you see that?

13 A. Yes.

14 Q. And you say: It's hard to shy away from that fact
15 even though I understand why.

16 A. Yes.

17 Q. Why? Why did you think they might be shying away
18 from that fact?

19 A. Well, they completed a study of their drug and wanted
20 to promote the effects of that drug at the meeting.

21 MR. STONE: No further questions.

22 THE COURT: All right. Thank you very much.

23 THE WITNESS: Thank you.

24 MR. GROOMBRIDGE: Vanda's next witness will be
25 Dr. Steven Bergmeier, again. He testified about invalidity

1 in the infringement part of the case and will now rebutting
2 on --

3 THE COURT: Okay.

4 MR. STONE: Your Honor, we had left open this
5 morning the evidentiary question about the prior BMS study
6 because Ms. Young wasn't here, and we were going to look at
7 the expert report. We may need to start with that if they
8 are still objecting to it.

9 THE COURT: Okay. What do we have to address?

10 MR. STONE: Where we were this morning is that
11 we would like to show the witness a prior art publication
12 that we maintain discloses BMS's process steps.
13 Mr. Rozendaal had objected to our doing so and had raised
14 the issue.

15 We had talked about where it arose in the expert
16 reports.

17 THE COURT: Right.

18 MR. STONE: They had at the time of the reports
19 been asserting that it was prior art and invalidated this
20 patent. And they've dropped that obviousness combination
21 and despite having argued that it invalidated the prior
22 art -- the patent as prior art, they now contend that we
23 haven't shown that it is prior art. And the issue was
24 whether this expert can testify to the fact that it is prior
25 art.

1 THE COURT: All right. Hold up.

2 What do you say to that, Mr. Rozendaal?

3 MR. ROZENDAAL: Your Honor, I think that the
4 issue -- so we have since this morning had a chance to look
5 at the report. There are what appear to be two
6 self-contradictory statements in the report at paragraphs --

7 THE COURT: Actually, what I want you to respond
8 to is what Mr. Stone said. Because one thing I don't know
9 is why don't you just introduce their prior contentions as
10 admissions.

11 MR. ROZENDAAL: Well --

12 THE COURT: I mean, if it's what you say it is,
13 and that's why I wanted Mr. Rozendaal to address
14 specifically what Mr. Stone just said, I mean, if you're on
15 record, even in the context of another patent in this case
16 asserting that this is prior art, why doesn't that just end
17 it?

18 MR. ROZENDAAL: What we have not asserted and
19 what they have not asserted is that this preference
20 represents the process used by BMS, and that's nowhere in
21 anyone's report on either side.

22 And that is -- that is the sticking point, Your
23 Honor, because they have told us that that is what they want
24 to use this for.

25 THE COURT: I see.

1 MR. STONE: If the prior art discloses the
2 process, it actually doesn't matter if it came from Dunkin'
3 Donuts. If the prior art --

4 THE COURT: I think what they are saying, the
5 way I interpret it, it goes to my question about, am I going
6 to need expert help to know is the prior art question
7 disclosing the BMS process.

8 MR. STONE: Fair enough. And let me separate
9 that into two pieces: The process and is it BMS's. Because
10 you might need expert testimony to say, that's a lot of
11 chemistry symbols, is that the process.

12 THE COURT: Right.

13 MR. STONE: You might also need -- this document
14 does say word "BMS" on it.

15 THE COURT: Okay.

16 MR. STONE: On the BMS issue, their expert,
17 Dr. Perni, conceded at his deposition that those people
18 worked at BMS at the time. We can profer that if we have
19 to.

20 THE COURT: On whether it's a process, you want
21 him to say, okay, now -- and so then it's very important is
22 it in the report. Okay. So then show me where it is in the
23 report.

24 MS. YOUNG: Your Honor, we have Dr. Bergmeier's
25 response to Dr. Perni's report as PTX-793. I can pass that

1 up to you.

2 THE COURT: All right.

3 MR. ROZENDAAL: Is that the September 29th
4 report? I don't have the PTX number. I'm sorry.

5 THE COURT: Is it in this white notebook that
6 was just handed to me? Because I don't see it.

7 MS. YOUNG: It is not, Your Honor. I did not --

8 THE COURT: Okay. Now are you all comfortable
9 discussing this in front of the doctor?

10 Okay.

11 MR. ROZENDAAL: Actually, Your Honor, I prefer
12 if we could --

13 THE COURT: Yeah, maybe it would be better, just
14 to be safe. I'm sorry I had to have you walk you up here,
15 but you can take a walk back. Thank you.

16 (Witness left the room.)

17 Okay. So where is it in the report?

18 MS. YOUNG: So, Dr. Bergmeier's report on Page
19 24, Paragraph 62 is where he starts responding to
20 Dr. Perni's arguments that Singh BMS's article was prior
21 art.

22 THE COURT: Paragraph what?

23 MS. YOUNG: Paragraph 62 is where it begins.

24 THE COURT: All right. Let me look at it.

25 Okay. What is the name of the prior art? Is

1 Singh the prior art?

2 MS. YOUNG: Singh is the prior art.

3 THE COURT: So the question is whether he gets
4 to talk about Singh?

5 MS. YOUNG: Yes, that's correct, Your Honor.

6 THE COURT: Okay. Well, so far he gets to talk
7 about Singh, at least something; so what is it specifically
8 he wants to say about Singh?

9 MS. YOUNG: So, specifically, what he wants to
10 say about Singh is it discloses the reducing and
11 propylinating steps that are in Claim 1.

12 THE COURT: Okay. Where is that?

13 MS. YOUNG: So if you turn to Page 7 of his
14 report, Paragraph 70.

15 THE COURT: Okay.

16 MS. YOUNG: Dr. Bergmeier states in his report
17 that Singh does disclose the contacting and the reacting
18 steps. Even though he says it discourages their use based
19 on the disclosures within Singh.

20 THE COURT: Okay.

21 MR. ROZENDAAL: Then in Paragraph 72 he says it
22 does not disclose those steps.

23 MS. YOUNG: I respectfully disagree about that
24 interpretation. That is talking about upstream reactions
25 and whether or not that had implications downstream.

1 MR. STONE: Your Honor, I would also add that
2 the first --

3 THE COURT: Whoa, whoa, whoa. Stop. Stop all
4 of you. I mean, I got to take my time and read this. I
5 mean, they don't look like -- it looks like in 70 he's
6 saying one thing and 72 he's not, I got to read it.

7 Give me a chance, please.

8 Okay. So here's how I read it, this is very
9 funny for the public. Here's what Paragraph 70 says:

10 Dr. Perni alleges that Singh discloses the
11 contact and reacting steps of Claim 1 of the '465 patent.
12 Singh does disclose as -- he means Singh "discloses," I'm
13 assuming there. Singh does disclose the contacting and
14 reacting steps.

15 So stop there, score one for Mr. Rozendaal.

16 But it continues: "...and explicitly
17 discourages their use."

18 Now it still discloses it, right?

19 MS. YOUNG: Right, that is our position.

20 MR. STONE: I think score one for our side.

21 Their expert says it discloses it, we say it
22 does. I think that it, to be fair, score one for our side.

23 THE COURT: Sorry, what? I missed you now. Now
24 I'm --

25 MR. STONE: We may be turned around, Your Honor.

1 Dr. Perni, in the first sentence, is
2 Mr. Rozendaal's expert.

3 THE COURT: Yeah.

4 MR. STONE: Mr. Rozendaal's expert alleges that
5 Singh, the piece we're talking about, discloses the
6 contacting and reacting steps. Our expert then agrees.

7 THE COURT: That's what I'm saying, he agrees
8 with him.

9 MR. STONE: You said score one for him, I think
10 at this point we're winning. At this point they are both
11 agreeing -- I may be misunderstanding Your Honor, but at
12 this point both experts agree it's in the prior art in
13 Singh. I know where the Court is going with the
14 contradiction, but you had said at this point score one for
15 his side. I think at this point score one for our side.
16 They say it's in the prior art and we agree.

17 THE COURT: Okay. Yes, I have got the parties
18 reversed.

19 So then he says: It does disclose it, which
20 would be mean he gets to talk about it's disclosed. But
21 explicitly discourages their use.

22 Now, then on page -- ten lines down or so he
23 writes: "Neither Singh nor ICH Q3A Guideline disclose this
24 limitation."

25 MS. YOUNG: And to put that in context, it's

1 with regard to --

2 THE COURT: I'm not finished.

3 MS. YOUNG: I'm sorry.

4 THE COURT: So he discusses it.

5 Now the objection is that he doesn't -- I mean,
6 he does discuss it.

7 MR. ROZENDAAL: Yes, I think it's fair to say he
8 does discuss it. He does not say anything about it being
9 from BMS or about BMS or anything having to do with BMS.

10 THE COURT: All right.

11 MR. ROZENDAAL: I think as long as we're clear
12 that he's not going to say anything at all about that, then
13 in light of what we're seeing here in the report I think --

14 THE COURT: Right. But here's the thing, he
15 gets to discuss what was disclosed, right.

16 So he gets to discuss, for instance -- and how
17 -- I don't think I could ever understand all this stuff, but
18 for instance that: Singh goes on to recommend an asymmetric
19 cyclopropanation process, which does not involved
20 (IR,2R)-2-(2,3-dihydrobenzofuran-4-yl)cyclopropane
21 carboxamide or
22 (IR,2R)-2-(2,3-dihydrobenzofuran-4-yl)cyclopropyl
23 methanamine.

24 He gets to discuss that and whatever else is
25 disclosed and maybe he even can explain it to me so I can

1 understand what it means. So he gets to talk about it.

2 Now, so there's no mention of BMS in this
3 Paragraph 70, there's no mention of BMS in Paragraph 71,
4 there's no mention of it in Paragraph 72, so he can't opine,
5 based on these three paragraphs, anything about BMS.

6 MS. YOUNG: I agree, Your Honor.

7 The issue is that we did not realize that they
8 were going to allege that Singh was not a BMS publication
9 because we thought we were in agreement about that.

10 THE COURT: Wait. That Singh was not -- okay.

11 MS. YOUNG: Because we had understood that there
12 was no dispute between the parties that the Singh authors
13 were working at BMS and it was a BMS paper.

14 MR. ROZENDAAL: I am not certain what basis
15 there was for that supposition, but in any event --

16 THE COURT: Is this the paper that somebody did
17 bring out; did you bring out in examining some witness that
18 Singh was associated with BMS?

19 MS. YOUNG: So Mr. Groombridge when examining
20 Dr. Perni asked whether or not the BMS work was publically
21 disclosed. And he said yes; consistent with his deposition.

22 In redirect, Ms. Wells elicited testimony that
23 caused some confusion, so then it became unclear whether or
24 not the work was public.

25 THE COURT: My point is, though, was there

1 questioning about the Singh article or was it just a general
2 statement that Mr. Groombridge put to Dr. Perni on cross and
3 he said, yeah.

4 MS. YOUNG: That's right. It was a general
5 statement because he said, yeah, we decided -- I believe it
6 was decided not to go forth in the interest of time, but it
7 is in the cross binder.

8 If it would be helpful --

9 THE COURT: When was Singh published?

10 MS. YOUNG: 2004.

11 THE COURT: All right. And just help me out
12 here, so Singh is published in 2004 and it discloses -- and
13 both sides are now contending it discloses the contacting
14 and reacting steps?

15 MS. YOUNG: Vanda agrees that it discloses the
16 contacting and reacting steps. When Dr. Bergmeier was asked
17 about it at his deposition, he also agreed.

18 THE COURT: Right, I guess -- and they're going
19 to say, well it's contingent argument. It discloses it. If
20 I read the patent, if I interpret contacting and reacting
21 the way plaintiffs want to.

22 MR. ROZENDAAL: Yes, Your Honor.

23 But I think the point is that if Vanda obtained
24 the process from BMS before the publication of this article,
25 then they still have an inventorship problem.

1 MS. YOUNG: And, Your Honor, we believe that is
2 a legal issue whether or not publically disclosed
3 information about 10 years before the patent was filed could
4 actually create an inventorship issue.

5 MR. ROZENDAAL: And we're happy to join --

6 THE COURT: Look, why don't we do this: It's
7 4:20, why don't we just let it in and I will just withhold
8 deciding whether I can make a determination that this
9 discloses the BMS. I mean, because maybe this is all going
10 to go away depending on claim construction.

11 MR. ROZENDAAL: Yes, Your Honor.

12 THE COURT: Let's just do that.

13 So I'm not ruling on admissibility, we'll --
14 unlike the other issue, we'll punt this one.

15 MR. ROZENDAAL: When it is offered, I expect to
16 renew my objection just for the record.

17 THE COURT: That's fine.

18 MS. YOUNG: Would it be helpful, Your Honor, to
19 have Dr. Perni's testimony on this issue?

20 THE COURT: You're going to call Dr. Perni?

21 MS. YOUNG: No, no, I'm just saying in terms of
22 what we had anticipated Dr. Perni to talk about regarding
23 the Singh article.

24 MR. STONE: Dr. Perni is their testimony, Your
25 Honor. The testimony in question is his deposition where he

DIRECT EXAMINATION - DR. BERGMEIER

1 said yes, this is from BMS.

2 MR. ROZENDAAL: Well, that's not in evidence.

3 THE COURT: Yeah. I don't understand what are
4 you trying -- you're just trying to admit it?

5 MS. YOUNG: I was just trying to help the Court
6 to provide some context for the Court, because in direct
7 examination we started to illicit this testimony. We
8 thought we had agreement on it and then on redirect is when
9 it became confused.

10 THE COURT: In direct --

11 MS. YOUNG: I'm sorry, in cross-examination.

12 THE COURT: Oh, of Dr. Perni?

13 MS. YOUNG: Of Dr. Perni. We believed we had
14 agreement on the issue and then on redirect is when we
15 understood there was confusion.

16 MR. ROZENDAAL: But he was asked nothing about
17 the Singh reference.

18 THE COURT: Right.

19 Okay. Let's just allow the testimony for right
20 now and we can debate what it proves later on.

21 (Dr. Bergmeier retook the stand.)

22 THE COURT: All right. And, Doctor, you remain
23 under oath.

24 THE WITNESS: Yes.

25 BY MS. YOUNG:

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. Welcome back, Dr. Bergmeier.

2 A. Thank you.

3 Q. Did you help prepare a demonstrative to assist in
4 your testimony today?

5 A. Yes, I did.

6 Q. Is that PDX-9 shown up on the screen?

7 A. Yes, it is.

8 Q. Have you been sitting in the courtroom this week
9 listening to testimony?

10 A. Yes, I have.

11 Q. Were you here in court yesterday for the testimony of
12 defendant's expert Dr. Perni?

13 A. Yes, I was.

14 Q. Did you agree with Dr. Perni's opinion that some
15 unknown person from BMS could have been named as an inventor
16 on the '465?

17 A. No, I did not -- No, I do not agree, I'm sorry.

18 Q. Did you help prepare slide two summarizing your
19 disagreements?

20 A. Yes, I did.

21 Q. What is that opinion?

22 A. My opinion is that Vanda conceived of the claimed
23 invention, they worked to identify impurities 1, 2, 3, 5 and
24 6 and to determine their importance in the manufacturing
25 process. And this is also indicative of BMS's failure to

DIRECT EXAMINATION - DR. BERGMEIER

1 conceive of this invention.

2 Similarly, BMS had no conception, they did
3 publically disclose methods to manufacture tasimelteon,
4 including methods with --

5 MR. ROZENDAAL: Objection, Your Honor,
6 undisclosed expert testimony.

7 THE COURT: Is this the same objection?

8 MR. ROZENDAAL: The very same objection.

9 THE COURT: I just wanted to make sure for the
10 record, it's noted and it will be ruled on later.

11 BY MS. YOUNG:

12 Q. Please continue, Dr. Bergmeier.

13 A. Including methods with a reducing step and a
14 propionylating step.

15 They did not identify any of Impurities 1, 2, 3,
16 5 or 6. And they really did not appreciate the process
17 concerns or the potential association with toxic compounds,
18 such phosgene.

19 Q. Did you agree with doctor --

20 THE COURT: Hold on. Stop for a second, sorry.

21 All right. Counsel, can I see you at sidebar.

22 (Whereupon, a discussion was held at sidebar as
23 follows:)

24 THE COURT: So the slide says that BMS
25 publically disclosed methods to manufacture tasimelteon,

DIRECT EXAMINATION - DR. BERGMEIER

1 including methods with a reducing step and a propionylating
2 step. Paragraph 70, 71 and 72 don't discuss the
3 propionylating step at all.

4 MR. ROZENDAAL: I think they might.

5 MS. YOUNG: I thought they did. I think we're
6 in agreement about that aspect.

7 THE COURT: Well, okay, if that's not an issue,
8 I just wanted to make sure because the quote -- and I'll
9 quote from Paragraph 70, it says: "Dr. Perni alleges that
10 Singh discloses the contacting and reacting steps of Claim
11 1..."

12 And then the next paragraph says: "Singh does
13 disclose the contacting and reacting steps..."

14 And then we have discussed about those two
15 steps, so I just want to make sure that your objection that
16 has nothing to do with that.

17 MR. ROZENDAAL: No, my objection is just whether
18 it was BMS or not.

19 THE COURT: Okay. Had nothing to do with that,
20 I wanted to make sure.

21 Good, all right, thank you very much.

22 (Whereupon, the discussion held at sidebar
23 concluded.)

24 BY MS. YOUNG:

25 Q. Dr. Bergmeier, did you agree with Dr. Perni's opinion

DIRECT EXAMINATION - DR. BERGMEIER

1 that Claim 10 of the '465 patent is obvious over either the
2 '529 patent or CN268 in view of the ICHQ3A guidelines?

3 A. No, I did not agree that these were obvious based on
4 either the '529 patent and the ICHQ3A guidelines or the
5 CN268 application and the Q3A guidelines.

6 Q. Are your opinions summarized on slide three?

7 A. Yes, they are.

8 Q. Can you please tell you us, at a very high level,
9 what those opinions are?

10 A. Yes. So the '529 patent did not disclose the
11 impurity, let alone Impurities 1 through 3, 5 and 6. They
12 didn't mention any process concerns or association with
13 other toxic compounds. And, consequently, there was no
14 motivation and no reasonable likelihood of success.

15 Similarly, the CN268 application did not
16 disclose Impurities 1, 2, 3, 5 and 6. And while they did
17 mention a relatively high impurity, that can still contain
18 significant amounts of Impurities 1, 2, 3, 5, and 6.

19 Again, no disclosure process concerns or
20 association with toxic compounds. And, again, no motivation
21 and no reasonable likelihood of success.

22 Q. All right. Before we get to those opinions, let's
23 talk about a person of ordinary skill in the art.

24 When coming to your opinions about what the
25 reducing step means and whether defendants infringe Claim 10

DIRECT EXAMINATION - DR. BERGMEIER

1 of the -- I'm sorry, whether or not Claim 10 of the '465
2 patent is invalid, did you consider who would be a person of
3 ordinary skill in the art?

4 A. Yes, I did. I defined it as a person having a
5 bachelor's degree in chemistry or organic chemistry or
6 related discipline.

7 Q. And are you a person of at least ordinary skill in
8 the art?

9 A. Yes, I am.

10 Q. Did you hear Dr. Perni's opinion of who a person of
11 ordinary skill in the art would be for the '465 patent?

12 A. Yes, I did.

13 Q. What do you understand of Dr. Perni's definition of a
14 person of ordinary skill?

15 A. It's a somewhat more complex definition. Someone
16 with more advanced degree, more skill, etc.

17 Q. Do you agree with Dr. Perni's definition?

18 A. No, I don't.

19 Q. On Slide 5, did you provide bullet points for
20 Dr. Perni's definition of a person of ordinary skill?

21 A. Yes, I did.

22 Q. What skill is being described in the first bullet
23 point?

24 A. It's education. So he suggested this person would
25 have a PhD in organic chemistry or related discipline.

DIRECT EXAMINATION - DR. BERGMEIER

1 Alternatively, having an undergraduate or master's degree
2 with considerable experience working in the field.

3 Q. Do you agree with that aspect of Dr. Perni's
4 definition?

5 A. No, I don't.

6 Q. Why not?

7 A. I've worked with people who have had my definition of
8 skill in the art and, similarly, the invention really
9 requires analyzing and determining structures.

10 Q. Are you a person of at least ordinary skill in the
11 art under that aspect of Dr. Perni's definition?

12 A. Yes, I am.

13 Q. Now, turning to the next bullet. Do you agree with
14 that aspect of Dr. Perni's definition?

15 A. No, I do not.

16 Q. Why not?

17 A. Someone who would have known or been aware of
18 relevant regulatory considerations. I don't think that
19 that's really a requirement. While it would be nice, it's
20 not a requirement.

21 One can certainly look these things up, but,
22 again, the invention is identifying compounds and
23 structures.

24 Q. Are you a person of at least ordinary skill in the
25 art under that aspect of Dr. Perni's definition?

DIRECT EXAMINATION - DR. BERGMEIER

1 A. Yes, I am.

2 Q. Would any of your opinions change if you applied
3 Dr. Perni's definition instead of own?

4 A. No, they would not.

5 Q. All right. Let's now turn to inventorship. Were you
6 in the courtroom when Dr. Perni testified that BMS had
7 publically disclose a synthesis of tasimelteon that
8 contained the two contacting and reacting steps of Claim 10
9 in response to Dr. Perni -- to Mr. Groombridge's question,
10 but then on redirect Ms. Wells took that back and he wasn't
11 sure because he assumed the IND was published?

12 A. Yes, I was.

13 Q. What was your understanding of whether or not BMS had
14 publically disclosed different methods for synthesizing
15 tasimelteon on that included the two contacting and reacting
16 steps of Claim 10, the reducing step and the propionylating
17 step?

18 MR. ROZENDAAL: Objection; undisclosed expert
19 testimony.

20 THE COURT: All right. I'll withhold ruling.
21 Go ahead. So for now you can answer.

22 THE WITNESS: I'm sorry, could you ask the
23 question again?

24 THE COURT: You don't need to object this time,
25 it's preserved.

DIRECT EXAMINATION - DR. BERGMEIER

1 MR. ROZENDAAL: Thank you, Your Honor.

2 BY MS. YOUNG:

3 Q. What was your understanding of whether or not BMS had
4 publically disclosed different methods for synthesizing
5 tasimelteon that included the two contacting and reacting
6 steps of Claim 10, the reducing step and the propionylating
7 step?

8 A. Yes, they did.

9 Q. And how had BMS disclosed that?

10 A. They disclosed it in a publication in early 2000, I
11 believe it was.

12 Q. So let's take a look at that. Can you turn in your
13 binder to the first tab, DTX-52?

14 A. Right.

15 Q. Do you recognize this document?

16 A. Yes, this is the publication that I was thinking of.

17 Q. Do you -- did you -- can we refer to that reference
18 as the Singh reference?

19 A. Yes.

20 Q. How did you become aware of the Singh reference?

21 A. In one of Dr. Perni's reports, he had cited this
22 paper and I subsequently went and looked this up.

23 Q. Did you consider the Singh reference in rendering
24 your opinions in this case?

25 A. Yes, I did.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. I'd like to offer DTX-52 into evidence.

2 MR. ROZENDAAL: Subject to the objections
3 previously stated, Your Honor.

4 THE COURT: All right. It's admitted
5 conditionally.

6 (DTX-52 was admitted.)

7 BY MS. YOUNG:

8 Q. Mr. Weir, can you put up DTX-52 on the screen.

9 And if you could blow up the title.

10 Who are the authors of this reference?

11 A. Ambarish Singh J. Siva Prasad and Edward Delaney. My
12 understanding is that they worked at BMS.

13 MR. ROZENDAAL: Objection; again, undisclosed
14 testimony. Nonresponsive. Move to strike.

15 THE COURT: You know what, just for right now,
16 keep objecting, because I did not think this is the way we
17 were getting to this as the process, but we are, so the --
18 so it's conditionally overruled, but it is conditionally and
19 I'll sort it out. Let's just go.

20 I mean, there's no foundation. I don't know how
21 he would know that this is the person, but it's
22 conditionally admitted. You do what you want, create the
23 record you think you need to create and I'm going to decide
24 afterwards.

25 MS. YOUNG: Your Honor, if it would be

DIRECT EXAMINATION - DR. BERGMEIER

1 helpful --

2 THE COURT: Don't ask me what's helpful, just do
3 what -- you do what your job is, it's 4:35, we need to move.

4 MS. YOUNG: Okay.

5 BY MS. YOUNG:

6 Q. When did this article get published?

7 A. 2004.

8 Q. Is that prior to the '465 patent?

9 A. I believe it is, yes.

10 Q. Let's turn to the next page and look at Page 2.

11 Do you see the section there entitled: Chemical
12 Approach Employed During Preclinical Research and
13 Development (Route A)?

14 A. Yes, I do.

15 Q. Mr. Weir, if you could blow that up as well as the
16 first paragraph under that header.

17 Dr. Bergmeier, what is being described here?

18 A. Basically, they're disclosing their preliminary
19 approaches to synthesizing a compound, which is tasimelteon.

20 Q. And Mr. Weir, if you could blow up -- go to Page 3
21 and blow up Figure 2 is this -- Dr. Bergmeier, is this the
22 reaction scheme for that route for the preclinical research
23 and development?

24 A. Yes, I believe it was.

25 Q. And in this route, is that there a propionylating

DIRECT EXAMINATION - DR. BERGMEIER

1 step?

2 A. Yes; that final step R.

3 Q. And what is compound 10?

4 A. Compound 10 is the methanamine or what we have been
5 referring to as the methanamine in the patent.

6 Q. And what is Compound 1?

7 A. Compound 1 is tasimelteon.

8 Q. Is there a carboxamide in this reaction scheme?

9 A. In this particular one, no there is no.

10 Q. So is there a reducing step?

11 A. There is a reducing step, but it's not of the
12 carboxamide.

13 Q. So there's not a reduction from the carboxamide to
14 the methanamine; is that fair?

15 A. Yes.

16 Q. How does this reaction scheme compare to what is
17 disclosed in BMS's '529 patent?

18 A. This is pretty much the same as was disclosed in the
19 '529 patent.

20 MR. ROZENDAAL: Objection, Your Honor;
21 undisclosed expert opinion.

22 THE COURT: Is this the same --

23 MR. ROZENDAAL: This is actually a slightly
24 different point.

25 THE COURT: Yeah. Is this disclosed?

DIRECT EXAMINATION - DR. BERGMEIER

1 MS. YOUNG: Your Honor, this was in response
2 to --

3 THE COURT: Are you pointing to the same
4 paragraphs?

5 MS. YOUNG: No, I was just trying to give some
6 context and then we're going to go to the synthetic route
7 where they are disclosing the --

8 THE COURT: All right. The objection then --
9 you have not been able to point to where it is in the expert
10 report, so the objection is sustained.

11 MR. ROZENDAAL: Move to strike, Your Honor.

12 THE COURT: It is struck.

13 BY MS. YOUNG:

14 Q. Okay. If we can go forward to Page 5 to section
15 entitled: Development of the Process Technology Support
16 Phase 2, 3 Clinical Studies and Future Commercialization
17 (Route C and D).

18 And Mr. Weir, if you could blow up the title for
19 Section 2.4, and the first four and five lines under that
20 header.

21 Dr. Bergmeier, what is being described here?

22 A. It's a route that they wanted to use to produce large
23 quantities of their drug candidate.

24 Q. And Mr. Weir, if we can now turn to Page 8, Figure 8
25 in this section. And if you could blow up that figure along

DIRECT EXAMINATION - DR. BERGMEIER

1 with its legend.

2 Dr. Bergmeier, what is being described in this
3 figure?

4 A. This is, I believe, the method that they were
5 mentioning in that previous heading.

6 Q. And is there a reducing step in this figure?

7 A. Yes, there is.

8 Q. Which one is it?

9 A. It's Step H. Treatment with -- of the carboxamide 24
10 with Red-Al followed by acid to generate the methanamine
11 salt Compound 10.

12 Q. And what is Compound 24?

13 A. Compound 24 is the carboxamide, which is what we see
14 in the patent under discussion.

15 Q. Is it fair to say that the carboxamide Compound 24 is
16 being reduced to the methanamine that is Compound 10?

17 A. Yes, it is.

18 Q. And is there a propionylating step in this reaction
19 scheme?

20 A. Yes, there is, it's Step J, treatment of the Compound
21 10 or the methanamine with propionyl chloride in the
22 presence of base to generate Compound 1.

23 Q. And what is Compound 1?

24 A. It's tasimelteon.

25 Q. And if we can now, Mr. Weir, go to Page 9 of this

DIRECT EXAMINATION - DR. BERGMEIER

1 document to the section headed: 2.5.

2 And if you could blow up the first paragraph
3 there.

4 Dr. Bergmeier, what is being described in this
5 section?

6 A. They're basically describing that, you know, there's
7 a lot of considerations in designing a synthesis for
8 basically the manufacturing in terms of cost for the process
9 as well as direct shortness of the path as well.

10 Q. All right. And Mr. Weir, if we could turn to Page
11 11, Figure 10, please. And blow that up along with the
12 legend.

13 Dr. Bergmeier, what is being shown here?

14 A. This is their, I believe, more or less final path to
15 Compound 1.

16 Q. And is there a reducing step and a propionylating
17 step in this reaction scheme?

18 A. Yes, there is. They don't actually draw or -- yes,
19 they don't actually draw the methanamine in this case, they
20 simply have the propionyl chloride.

21 Q. Let's start with -- okay. Let's go with the
22 propionyl chloride, does that correspond to a letter in this
23 scheme?

24 A. Yes, it's (h).

25 Q. And is there a disclosure of a reducing step in this

DIRECT EXAMINATION - DR. BERGMEIER

1 scheme?

2 A. Yes, there is. It's step F treatment with LAH or
3 lithium aluminum hydride followed by HCL.

4 Q. And Mr. Weir, if we could turn to Page 12 and blow up
5 that first full paragraph there.

6 And if you could focus on the last sentence,
7 what's being -- or the last two sentences, what is being
8 described here, Dr. Bergmeier?

9 A. Basically they're indicating that the dropout of
10 clinical candidates is fairly high. And basically the
11 majority of the processes that are actually developed for --

12 MR. ROZENDAAL: Objection; undisclosed expert
13 opinion. I don't know what that is about.

14 THE COURT: Where is this disclosed in the
15 expert report?

16 MS. YOUNG: This is just the conclusion of the
17 paper, Your Honor. I was just trying to conclude about the
18 paper and what the paper discloses.

19 THE COURT: It's just the conclusion of Singh?

20 MS. YOUNG: Yes, that's correct.

21 THE COURT: I'll right now let it in
22 conditionally.

23 THE WITNESS: So they're just noting that many
24 of the methods that are designed for making a clinical
25 candidate never actually reach a production stage. And they

DIRECT EXAMINATION - DR. BERGMEIER

1 note that the process described above was just such a case.

2 BY MS. YOUNG:

3 Q. And what is the melatonin agonist one that is
4 referenced there?

5 A. It's tasimelteon.

6 Q. Okay. Let's now turn to Vanda's work. If you could
7 turn to the next tab in your binder, it should be labeled
8 PTX-299.

9 A. Okay.

10 Q. Do you recognize this document?

11 A. Yes.

12 Q. What is this document?

13 A. This is specification change history that Vanda was
14 supplying to the FDA.

15 Q. Is this one of the documents you reviewed in
16 rendering your opinions?

17 A. Yes, it was.

18 Q. We'd like to offer PTX-299 into evidence.

19 MR. ROZENDAAL: No objection, Your Honor.

20 THE COURT: It's admitted.

21 (PTX-299 was admitted.)

22 BY MS. YOUNG:

23 Q. Dr. Bergmeier, did you prepare slide 7 with
24 annotations to Page 2 of PTX-299?

25 A. Yes, I did.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. Dr. Bergmeier, what are you showing here?

2 A. This is part of that overall table listing the
3 specification change history. At the bottom there in 2011 I
4 note that Vanda indicated that at that point in time they
5 had identified Impurities 1, 2 and 3. But it was not until
6 approximately two years later that the Impurities 5 and 6
7 had been identified and were added into their specification
8 sheet.

9 Q. What is the significance of that?

10 A. Really just that it was not a trivial process to
11 identify these Impurities 1, 2, 3, 5 and 6, and it did take
12 time and effort on Vanda's part to identify those compounds.

13 Q. Now let's turn to the next tab in your binder,
14 JTX-117. And I believe these documents have already been
15 admitted into evidence.

16 Dr. Bergmeier -- Mr. Weir, if you could put it
17 up on the screen.

18 Dr. Bergmeier, what is this document? I'm
19 sorry, JTX-117?

20 A. This is part of the chemistry manufacturing control
21 report that BMS had submitted to the FDA.

22 Q. And Mr. Weir, if you could blow up the top portion
23 there, which submission is this?

24 A. I believe this is number four.

25 Q. And if we could then turn to Page 24 of this

DIRECT EXAMINATION - DR. BERGMEIER

1 document, please.

2 And Mr. Weir, if you could blow up the top
3 portion of this document.

4 Which submission is this, Dr. Bergmeier?

5 A. This is submission number 7.

6 Q. And if we could turn to Page 47 of this document,
7 please.

8 What is shown on this page?

9 A. Okay. So this is their impurities specification. So
10 down at the bottom there you'll note that they're allowing
11 up to 1 percent of an individual impurity and up to
12 3 percent of total impurity.

13 Q. Had these specifications changed at all from BMS's
14 original IND?

15 A. I don't believe it has.

16 Q. Did you prepare Slide 8 of PTX-098?

17 A. Yes, I did.

18 Q. And does it include the specifications from BMS's
19 original IND and BMS's amendment to number seven?

20 A. Yes, it is.

21 Q. Mr. Weir, could you put that up on the screen,
22 please.

23 Dr. Bergmeier, what are you showing here?

24 A. Well, again, the individual impurity is just limited
25 to 1 percent and total impurity is up to 3 percent.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. Let's focus our attention now on Impurities 1 through
2 3, 5, and 6 in Slide 9.

3 What is your opinion about whether BMS had
4 identified Impurities 1 through 3, 5, and 6?

5 A. They did not, so if you look on the right-hand column
6 there, there's work done at Formosa for Vanda, you'll note
7 they had identified Impurities 1 and 2, BMS had not seen
8 those in their HPLC analysis. They also identified a
9 compound Impurity 5, which they thought might co-elute with
10 what BMS called your Impurity P5, and then they also
11 identified Impurities 3 and 6, which, again, BMS had not
12 seen in their HPLC studies at all.

13 Q. I see the chart that you have highlighted is from
14 PTX-811, so let's take a look at that document.

15 MS. YOUNG: And I believe this document has
16 already been entered into evidence, Mr. Weir if you could
17 put that on screen and...

18 BY MS. YOUNG:

19 Q. Dr. Bergmeier, what is this document?

20 A. Again, this is from Formosa, again, just potential
21 impurities that were identified in Vanda's tasimelteon
22 product.

23 Q. And if we could blow up the top of the screen,
24 Mr. Weir, I think Dr. Bergmeier you said Formosa, is this
25 from Vanda's NDA?

DIRECT EXAMINATION - DR. BERGMEIER

1 A. Yes.

2 Q. And if we could turn now to -- and Mr. Weir, if you
3 could blow up the second paragraph in the bottom.

4 What did Vanda tell FDA about P5?

5 A. So they noted that P5 was identified at BMS from
6 LC/MS and LV/NMR data as described in their IND amendment
7 number seven.

8 Q. Was that the document we were just looking at?

9 A. Yes.

10 Q. If we could go back and look at that particular --
11 those particular pages then.

12 Mr. Weir, if you could go back to JTX-117. And
13 I believe Page 54 of that document corresponds to Page 29 of
14 BMS's amendment number seven.

15 What tentative structure did BMS identify for
16 P5?

17 A. So the structure on the lower left was the structure
18 that BMS had tentatively identified as P5.

19 Q. How many RRTs are associated with that?

20 A. They associated three RRTs with that. They said that
21 they were possibly stereoisomers of that original structure
22 there.

23 Q. Do you understand those RRTs to be different
24 impurities?

25 A. Yes.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. Did you prepare a demonstrative, which is comparing
2 the structures of Impurity 5 to the proposed structures of
3 those RRT impurities?

4 A. Yes, I did.

5 Q. And Mr. Weir, if we could go to PDX-09.10.

6 What is being shown here?

7 Oh, I'm sorry, PDX-09, Slide 10?

8 A. There we go.

9 Q. What is being shown here?

10 A. Okay. So, again, we've got the tentative structure
11 that BMS had proposed on the left-hand side of the slide
12 there. Whereas on the right-hand side, we have the correct
13 structure of -- that Vanda had determined for Impurity 5.

14 So they are similar, but they are different.

15 Q. How are they different?

16 A. The BMS structure, basically they drew a line, a
17 chemical bond between two carbons to essentially show that
18 they believed this to be a dimeric product.

19 Vanda, again, has a bond between two carbons
20 there in different places to form a different dimeric
21 structure.

22 Q. And when you say it has a different dimeric structure
23 and bond, are you referring to the line from P3 on the
24 bottom structure there?

25 A. Yeah. So we're talking about this bond right here

DIRECT EXAMINATION - DR. BERGMEIER

1 versus this bond right here. So they're basically joining
2 those two, sort of, identical pieces together at different
3 spots on those two halves of the molecule.

4 Q. And do you see in BMS's figure there's a reference to
5 LC/MS?

6 A. Yes.

7 Q. What is that?

8 A. Basically the LC/MS is going to give you the mass of
9 the molecule that elutes at that relative retention time,
10 but we would expect that the mass of the compound of both of
11 those compounds would be the same; they would have the same
12 chemical formula, same number of carbons, hydrogens and
13 nitrogens and oxygens, but the connectivity between those
14 carbons, hydrogens, nitrogens and oxygens is going to be
15 different.

16 Q. Do you see reference to LC/NMR?

17 A. Yes.

18 Q. What --

19 A. NMR is typically used to identify that connectivity
20 between hydrogens and carbons. And we're looking at a -- I
21 would call it a subtle difference between these two
22 molecules. And without really probably fairly extensive NMR
23 examination, you may not make the correct structural
24 determination here.

25 I might add that the structure that Vanda

DIRECT EXAMINATION - DR. BERGMEIER

1 proposed is -- seems to be chemically much more correct.

2 There's, I believe, multiple proposals as to how it might be
3 formed. I don't think anyone has come up with a good
4 proposal as to how P5 might be formed.

5 Q. What is your opinion then of whether BMS should be an
6 inventor on the '465 patent?

7 A. They really did not identify Impurities 5, 6, 1, 2,
8 or 3 so, no, I do not think that they should be an inventor.

9 Q. What about the first part of the claim; the contact
10 and the reacting steps?

11 A. My opinion is that they had already publically
12 disclosed this --

13 MR. ROZENDAAL: Objection, Your Honor. Same
14 undisclosed testimony.

15 THE COURT: All right. Conditionally overruled.

16 THE WITNESS: And so, no.

17 BY MS. YOUNG:

18 Q. Dr. Bergmeier, let's now turn to your obviousness
19 opinions.

20 What is your understanding of what's in dispute
21 with regard to Claim 10 with respect to obviousness?

22 A. The composition that comprises up to or .15 percent
23 or less of Impurities 5, 6, 1, 2 and 3.

24 Q. Did the Patent Office consider any of the references
25 relied on by Dr. Perni?

DIRECT EXAMINATION - DR. BERGMEIER

1 A. Yes, they did.

2 Q. Did you prepare a demonstrative, Slide 14,
3 highlighting the front page of the '465 patent?

4 A. Yes, I did.

5 Q. Which references did the Patent Office consider?

6 A. They examined the '529 patent. They also examined
7 the FDA, Q3A guidelines, which is quite similar to the ICH
8 guidelines, they also examined a Chinese patent, the '019
9 patent.

10 Q. Dr. Bergmeier, did you review documents to determine
11 what Vanda said to the Patent Office with regard to some of
12 these references?

13 A. Yes, I did.

14 Q. If you could turn now in your binder to the tab
15 labeled PTX-830.

16 Do you recognize this document?

17 A. Yes, I do.

18 Q. What is this document?

19 A. This is a response from Vanda to the U.S. Patent
20 Office.

21 Q. Did you consider that document in rendering your
22 opinions?

23 A. Yes, I did.

24 MS. YOUNG: We'd like to offer PTX-829 into
25 evidence.

DIRECT EXAMINATION - DR. BERGMEIER

1 MR. ROZENDAAL: No objection.

2 THE COURT: It's admitted.

3 (PTX-829 was admitted.)

4 BY MS. YOUNG:

5 Q. Mr. Weir, if you could put that up on screen,
6 PTX-830, and if you could go to Page 7 under section 1 in
7 that first paragraph.

8 What is being disclosed here?

9 A. The Patent Office had rejected Claims 1 through 19,
10 23, 24 and 38.

11 Q. Based on which references?

12 A. Basically, the Chinese patent '019 and Catt or the
13 '529 patent.

14 Q. And now let's turn to the next page.

15 And Mr. Weir, if you could blow up the last two
16 paragraphs.

17 How did Vanda respond to the Patent Office?

18 A. Well, they noted that these impurities were not
19 previously known according to the method described in the
20 '529 patent. And really without the patent application
21 here, no one would have known that such impurities could be
22 formed or present in the product.

23 Q. What did the Patent Office think of Vanda's response?

24 A. I believe that they allowed it eventually.

25 Q. Okay. And if we could turn to the next document in

DIRECT EXAMINATION - DR. BERGMEIER

1 your binder, which should be PTX-829.

2 Do you recognize this document?

3 A. Yes.

4 Q. What is that document?

5 A. Again, a response from Vanda to the U.S. Patent
6 Office.

7 Q. Did you consider this document in rendering your
8 opinions?

9 A. Yes, I did.

10 MS. YOUNG: We'd like to offer PTX-830 into
11 evidence.

12 MR. ROZENDAAL: No objection.

13 THE COURT: All right. It's admitted.

14 (PTX-830 was admitted.)

15 BY MS. YOUNG:

16 Q. If we could turn to Page 5 -- and Mr. Weir, if you
17 could put that up on the screen to the third paragraph,
18 please.

19 What is Vanda responding to here?

20 A. Again, I believe this patent was initially rejected.

21 Q. And what was the basis of that rejection?

22 A. Again, they noted it was clearly anticipated by the
23 '529 patent.

24 Q. And how did Vanda respond -- and Mr. Weir, if you
25 could blow up the bottom half of that paragraph.

DIRECT EXAMINATION - DR. BERGMEIER

1 I'm sorry, the next paragraph.

2 How did Vanda respond?

3 A. Well, again, they noted that these impurities were
4 not disclosed in the '529 patent. And they really could not
5 have even known that they were in the -- in their
6 preparation of the compounds.

7 Q. What did the Patent Office think of this response?

8 A. Again, eventually this patent was allowed.

9 Q. And Mr. Weir, if we can go back to the demonstrative
10 slides, and if you could put up slide 17, please.

11 Did you hear Dr. Perni's testimony regarding the
12 '529 patent?

13 A. Yes, I did.

14 Q. Did you agree with Dr. Perni that the '529 patent has
15 no reference to the impurity of tasimelteon and has no
16 reference to Impurities 1 through 3, 5 and 6?

17 A. Yes, I did.

18 Q. Let's now turn to the ICH guidelines, which is
19 DTX-555, which I believe is also into evidence.

20 What does ICHQ3A disclose?

21 A. Provides guidelines as to how to deal with impurities
22 in your drug product.

23 Q. Did you prepare Slide 18 to go through a bit of what
24 the ICHQ3A provides?

25 A. Yes.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. What is being shown on Slide 18?

2 A. Basically, this is sort of the decision tree that's
3 listed in the guidelines that, sort of, sets out how you
4 might approach knowing the structure, not knowing the
5 structure, how much you have, etc., and how you might deal
6 with those things.

7 Q. What happens if you know the structure of an
8 impurity?

9 A. Your path is somewhat simpler; in that, you can
10 simply, in a way, just sort of move ahead and make sure that
11 as long as you know the impurity, you might be able to
12 purify out that impurity knowing the structure of that
13 compound.

14 Q. What happens if you do not know the structure?

15 A. Well, actually, as Dr. Perni noted, your path forward
16 is much more onerous; in that, you need to figure out how to
17 either remove the impurities without really knowing what
18 they are or carry out additional toxicity studies on those
19 impurities.

20 Q. Is there anything in ICHQ3A that would point a person
21 of ordinary skill to Impurities 1 through 3, 5 or 6?

22 A. No, there is not.

23 Q. Did you prepare Slide 19 summarizing your opinions
24 about the '529 and the ICHQ3A guidelines?

25 A. Yes, I did.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. What are you disclosing here?

2 A. Well, essentially, the '529 patent and the ICH
3 guidelines don't have any information about potentially
4 impurities of tasimelteon, let alone are the claimed
5 Impurities 1, 2, 3, 5 and 6. They really don't provide any
6 motivation to identify those compounds nor their structure.
7 And there is no reasonable expectation of success for
8 identifying these compounds based on those general
9 informations provided in the '529 patent or the ICH
10 guidelines.

11 Q. Let's turn to Dr. Perni's second obviousness
12 combination, which is CN268 and ICHQ3A guidelines.

13 Do you agree with Dr. Perni that CN268 only
14 mentions purity in a couple of places and does not include
15 any information as to how long the purified tasimelteon --

16 A. Yes, I do.

17 Q. And do you also agree with Dr. Perni that CN268
18 discloses tasimelteon, but the highest purity discloses 99.6
19 pure?

20 A. Yes. You know, the claimed purity is fairly high,
21 but that still could contain a significant amount of
22 Impurities 1, 2, 3, 5 or 6.

23 I should also point out that the melting point
24 was relatively low relative to the melting points that have
25 been reported for tasimelteon, as well as the aqua flow

DIRECT EXAMINATION - DR. BERGMEIER

1 rotation is quite low relative to the known aqua flow
2 rotation of tasimelteon, which might indicate that the
3 purity might not really be quite as good as they are
4 claiming.

5 Q. And do you agree with Dr. Perni that CN268 does not
6 mention Impurities 1 through 3, 5 or 6?

7 A. I do agree it does not mention any of those
8 impurities.

9 Q. Did you provide a slide summarizing your opinions
10 with regard to Dr. Perni's second obviousness combination?

11 A. Yes.

12 Q. Is that Slide 23?

13 A. Yes.

14 Q. What is your opinion with regard to whether or not
15 the '468 patent is obvious in view of CN268 and ICHQ3A
16 guidelines?

17 A. Well, again, the CN268 application and the ICH
18 guidelines combined don't have any information about
19 potential impurities, much less the structures of these
20 Impurities 1, 2 3, 5 and 6.

21 They don't provide any motivation to identify
22 those impurities, much less their structure.

23 And, again, no reasonable expectation success
24 for identifying those impurities based on those general
25 disclosures in the Chinese application or the ICH

DIRECT EXAMINATION - DR. BERGMEIER

1 guidelines.

2 Q. I understand you considered other factors or
3 secondary considerations as to whether Claim 10 of the '465
4 patent is nonobvious?

5 A. Yes, I did.

6 Q. What other facts or factors did you consider?

7 A. I looked at the FDA response letters to both Teva and
8 Apotex.

9 Q. If you could turn to the second-to-the-last tab in
10 your binder. It should be labeled PTX-153.

11 Do you recognize this document?

12 A. Yes, I do.

13 Q. What is this document?

14 A. This is the response letter to Teva and their
15 manufacturer Watson Pharmaceuticals regarding their
16 application.

17 Q. Is this one of the documents you reviewed in
18 rendering your opinions?

19 A. Yes, it is.

20 MS. YOUNG: We'd like to offer PTX-153 into
21 evidence.

22 MR. ROZENDAAL: No objection.

23 THE COURT: All right. It's admitted.

24 (PTX-153 was admitted.)

25 BY MS. YOUNG:

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. Mr. Weir, could you put PTX-153 on the screen.

2 Do you see on the top there it says: Complete
3 response?

4 A. Yes.

5 Q. What is a complete response letter?

6 A. Basically responding to everything that they have
7 presented to the FDA and they are letting them know if what
8 they have submitted is adequate.

9 Q. And if, Mr. Weir, you could blow up the second
10 paragraph of this letter.

11 What is FDA saying to Teva?

12 A. They said that your submission is not adequate in its
13 present form and they provided recommendations to address
14 the issues.

15 Q. And Mr. Weir, if we could go to --

16 THE COURT: Ms. Young, how much longer do you
17 have?

18 MS. YOUNG: I have maybe five more minutes.

19 THE COURT: Okay.

20 BY MS. YOUNG:

21 Q. Maybe it's easiest just to get to the slide then.

22 Mr. Weir, if you could pull up PDX-09, Slide 25.

23 Is this a slide you made highlighting what FDA
24 said to Teva with regard to Impurities 1, 2, 3, 5 and 6?

25 A. Yes, it is.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. What did FDA ask Teva to do?

2 A. They asked them to basically let them know whether or
3 not the following impurities, which are the ones that are a
4 noted in the patent -- or '465 patent, I'm sorry. And
5 whether or not they could detect them. And if so, how they
6 are controlling for those compounds.

7 Q. Do you see a reference there to US20170190683A1?

8 A. Yes.

9 Q. Do you have an understanding of what that is?

10 A. Yeah, I believe that is the patent application for, I
11 believe, the '977 patent.

12 Q. And how is the '977 patent related to the '465
13 patent?

14 A. It's the parent patent of the '465 patent, I believe
15 it's called.

16 Q. And how did Teva respond to FDA's complete response
17 letter?

18 A. They indicated that they could either quantitate
19 these individual impurities or that their method was capable
20 -- or their method was not going to form those impurities.

21 Q. And how was Teva able to quantitate those impurities?

22 A. By knowing the structure, they were able to basically
23 make some of those impurities independently and spike their
24 samples with those impurities to determine whether or not
25 they were actually in there.

DIRECT EXAMINATION - DR. BERGMEIER

1 Q. It stands to reason that Teva would not have been
2 able to do that if they didn't know the structure?

3 A. If you did not know the structure, you would not be
4 able to do that.

5 Q. Why wouldn't it have been sufficient for the
6 specification to be less than 0.10 percent of any unknown
7 impurities; why wouldn't that be sufficient?

8 A. It's important to be able to control your process to
9 make sure that you're not making those as well.

10 Q. If we could turn to the last slide.

11 Did FDA ask the same thing of Apotex?

12 A. Yes, they did.

13 Q. And how did Apotex respond?

14 A. Again, they noted that they would be able to identify
15 those compounds in the HPLC or else control for their
16 presence by -- through their process.

17 Q. And how did -- how was Apotex able to determine
18 whether or not they were able to find these impurities by
19 HPLC?

20 A. Again, they have the structure, so they could make
21 them separately and analyze them by HPLC. But they were
22 also able to control their process so that some of these
23 things were not made.

24 MS. YOUNG: I believe this document is already
25 in evidence.

CROSS-EXAMINATION - DR. BERGMEIER

1 MR. COBLENTZ: There's no objection.

2 MS. YOUNG: I have no further questions.

3 THE COURT: You're moving it? Just in case --

4 MS. YOUNG: I'm sorry it's JTX-071.

5 THE COURT: All right. It's admitted.

6 MS. YOUNG: Thank you.

7 (JTX-071 was admitted.)

8 THE COURT: All right.

9 How long are you going to be in cross?

10 MR. ROZENDAAL: I don't know 20 minutes.

11 THE COURT: All right. Let's go ahead.

12 CROSS-EXAMINATION

13 BY MR. ROZENDAAL:

14 Q. Good afternoon, Dr. Bergmeier.

15 A. Good afternoon.

16 Q. Dr. Bergmeier, why don't we start with some
17 impurities?

18 A. Okay.

19 Q. And could you turn in your black binder, please, to
20 DTX-073, which is in evidence.

21 And if we could go, please, to 73.9, Page 9.

22 Dr. Bergmeier, the second sentence of this
23 section says that: The chromatographic conditions used by
24 three manufacturers of tasimelteon to measure related
25 substances in tasimelteon drug substance are essentially

CROSS-EXAMINATION - DR. BERGMEIER

1 identical.

2 Do you see that?

3 A. Yes.

4 Q. That's what -- that's what Vanda told the FDA about
5 the impurity detection procedures used by the various
6 manufacturers, right?

7 A. Right.

8 Q. And you agree with that, right?

9 A. Yeah.

10 Q. It says: "Therefore, a direct comparison of the
11 impurities present in the tasimelteon drug substance lots
12 and the level of each impurity can be performed."

13 Did I read that correctly?

14 A. Yes.

15 Q. And you agree with that, right?

16 A. Yeah, sort of.

17 Q. Sort of?

18 A. There can be inconsistencies in columns even when
19 they are nominally the same column. Length of time in
20 between when these were done and when they were done years
21 ahead of time could lead to changes that maybe we weren't
22 really aware of.

23 Q. You're not saying it would be inappropriate to make
24 the comparison that Vanda made in this document submitted to
25 the FDA, though, are you?

CROSS-EXAMINATION - DR. BERGMEIER

1 A. No, not really.

2 Q. Okay. So let's go ahead then, Mr. Brooks, and pull
3 up the table that goes at the bottom of that page and on to
4 the top of the next page. See if we can kind of stack it up
5 together a little bit.

6 This is -- again, this is the comparison of the
7 retention time data for impurities in various manufacturers
8 of tasimelteon, right?

9 A. Yes.

10 Q. And this kind of data comes from HPLC; is that right?

11 A. Yes.

12 Q. Okay. And HPLC can be used to detect impurities even
13 if the structural identity of those impurities is not known?

14 A. It can be used to detect an impurity, but you may not
15 know what it is.

16 Q. Right. So you can detect the presence of the
17 impurity without knowing the structural identity of the
18 impurity, right?

19 A. You can detect an impurity, you may not know what it
20 is.

21 Q. I'm having trouble understanding what we're
22 disagreeing about.

23 So the way HPLC works is you put a sample into a
24 column and different components of the sample come out at
25 different speeds, right?

CROSS-EXAMINATION - DR. BERGMEIER

1 A. Yes.

2 Q. And it's the time that it takes for the different
3 components of the sample to make it through the column that
4 is being reported here in this table from DTX-73, right?

5 A. Yes.

6 Q. And it is possible to detect the presence of the
7 various impurities in this table even if -- even if one does
8 not know the contents of the peak on the chromatogram; is
9 that a fair way of putting it?

10 A. Yes, but you can have co-elution.

11 Q. Oh, I see, so your point is it's possible that two
12 things can come out close in time?

13 A. Yes.

14 Q. Or something could come out close in time with the
15 drug product that you're looking at?

16 A. Yes.

17 Q. Okay. Now, there's no evidence that you've seen in
18 this case that co-elution was an issue with Impurities 1
19 through 3 or 5 and 6 that are at issue in this case?

20 A. I don't believe that they indicated that there was an
21 issue with this particular set of studies.

22 Q. Okay. Now, if we look in -- the first column here
23 talks about -- the third row talks about Impurity 7.

24 Do you see that?

25 A. Right.

CROSS-EXAMINATION - DR. BERGMEIER

1 Q. That's currently not at issue in the case, right?

2 A. I believe that's correct.

3 Q. But it's one of the identified impurities.

4 And when BMS identified that impurity, they
5 called it Impurity P1, right?

6 A. Yes.

7 Q. So Impurity 7 and Impurity P1 you see next to each
8 other on the table are the same thing, right?

9 A. Yes.

10 Q. So a person reading this would know that they're --
11 referring to the same thing?

12 A. Yes.

13 Q. All right. So then -- but then we go down to
14 Impurity 5 in the table. And next to that is Impurity P5,
15 right?

16 A. Right.

17 Q. And so your testimony is that the evidence that
18 you've looked at has revealed that Impurity P5, as you read
19 the data, is different from Impurity 5?

20 A. Yes.

21 Q. Right. And so what I'm trying to figure out is is it
22 your testimony that Vanda just made a mistake when it told
23 the FDA, when it put them sort of next to each other in a
24 table like this just like it did for Impurity 7 and Impurity
25 P1?

CROSS-EXAMINATION - DR. BERGMEIER

1 A. I don't know that Vanda made any mistakes. I think
2 that they noted that BMS had identified something called P5.
3 It was later, I believe, that they found the structure of
4 what P5 was or Impurity 5 was, which was different from what
5 BMS had tentatively identified it as.

6 Q. Okay. But a fair reading of this table is that this
7 is Vanda telling the FDA that they're the same thing, right?

8 A. They thought they were the same thing.

9 Q. Okay. And so -- but you just think they were wrong
10 about that?

11 A. I mean, they subsequently showed that they were not
12 the same compound.

13 Q. Do you know if they ever informed the FDA about the
14 difference between those two impurities?

15 A. I do not know.

16 Q. Okay. Now, let's go back to the previous page of the
17 document, DTX-73.8, please, Mr. Brooks.

18 And if we go down to the next to the last
19 paragraph. And we look at the second line, this is one that
20 you directed our attention to on your direct exam, right.

21 It says impurities P2, P3, P4 and P5 were
22 identified at BMS from LC/MS and LC/NMR data, right?

23 A. Yes.

24 Q. And LC/MS is liquid chromatography mass spectrometry,
25 right?

CROSS-EXAMINATION - DR. BERGMEIER

1 A. Yes.

2 Q. And LC/NMR is liquid chromatography followed by
3 nuclear magnetic resonance, right?

4 A. Yes.

5 Q. And those are the standard tests you use to identify
6 a chemical structure, right?

7 A. Yes.

8 Q. BMS was not doing anything out of the ordinary here?

9 A. No.

10 Q. All right. And you expect those typically to be
11 reliable ways of identifying a structure?

12 A. They can be prone to interpretations, especially NMR.

13 Q. Okay. But generally this is what you would expect to
14 use. It's not like they chose some exotic test that's
15 outside the mainstream for this sort of analysis, right?

16 A. No.

17 Q. All right. And then -- now you say that the
18 structure in -- let's see, I think we may have an issue --
19 Mr. Brooks, would you pull up JTX-117 and look at Page 54.

20 All right. And you had identified what you
21 think was the structure of P5 as this structure in the lower
22 left-hand corner; is that right?

23 A. I believe that's what BMS proposed for P5, yes.

24 Q. Right. But we can agree that nothing in this
25 document talks about P5, right; it doesn't say P5?

CROSS-EXAMINATION - DR. BERGMEIER

1 A. No.

2 Q. You have pieced together that this is what you think
3 they think P5 was?

4 A. Yes.

5 Q. Okay. Now, it was known in the prior art before the
6 '465 patent that pharmaceutical products needed to be
7 analyzed for impurities, right?

8 A. Yes.

9 Q. And it was also known that limiting impurities in
10 drug substances like tasimelteon is something important;
11 yes?

12 A. Yes.

13 Q. And a drug manufacturer would typically use HPLC to
14 detect the impurity?

15 A. Yes.

16 Q. Right. And one can also determine the quantity of
17 the impurity based on HPLC, right?

18 I need a verbal answer.

19 A. Yes.

20 Q. And we agree that people of skill in the art would
21 have known how to adjust the HPLC conditions to separate
22 individual impurities, right?

23 A. It's not always easy.

24 Q. Is that a yes or a no?

25 A. Generally, you know, you can adjust the conditions to

CROSS-EXAMINATION - DR. BERGMEIER

1 separate most impurities.

2 Q. So generally, yes? More often than not, yes?

3 A. I don't know about more often than not, but I think
4 generally, yes.

5 I would note that I believe it was Teva or
6 perhaps Apotex, I forget which one, did note that Impurities
7 3 and 5 did co-elute.

8 Q. Okay. But the separation -- the adjusting of HPLC
9 conditions to separate individual impurities is something
10 generally within the skill of a person of skill in the art?

11 A. Yes.

12 Q. This is what people who work with HPLC do everyday,
13 right?

14 A. Yes.

15 Q. And the patent doesn't discuss any special conditions
16 for detecting Impurities 1 through 3, 5 and 6, right?

17 A. No.

18 Q. It doesn't tell you at all how to adjust your machine
19 to find these things?

20 A. No.

21 Q. It assumes that you'll know how to adjust the HPLC to
22 detect them, right?

23 A. I would say so, yes.

24 Q. Now, it's -- it would be -- at the time of the
25 invention -- strike that. Let me start that again.

CROSS-EXAMINATION - DR. BERGMEIER

1 At the time of the invention would someone
2 making -- someone making tasimelteon for pharmaceutical use
3 would be motivated to keep the quantity of each impurity
4 below 0.15 percent, right?

5 A. Yes.

6 Q. And people of skill in the art before the '465 patent
7 had not previously thought that Impurities 1 through 3, 5
8 and 6 were an issue or a problem for the synthesis of
9 tasimelteon, right?

10 A. Yes.

11 Q. And at the time of the invention there were
12 regulatory requirements for the amount of impurities that
13 were allowed in a drug substance, right?

14 A. Yes.

15 Q. And at the time of the invention, the FDA had
16 recognized the ICH guidelines on impurities, correct?

17 A. Yes.

18 Q. And ICHQ3A guideline includes specific thresholds for
19 identifying impurities and qualifying impurities and
20 reporting impurities, right?

21 A. Right.

22 Q. I'm sorry, did you --

23 A. Yes.

24 Q. Thank you.

25 So let's go ahead and take a look at those

CROSS-EXAMINATION - DR. BERGMEIER

1 thresholds.

2 Can we bring up, Mr. Brooks, DTX-55 at Page 12.

3 You're welcome to follow along in your binder,
4 Doctor, but I think you'll recognize these numbers on the
5 screen.

6 A. Yes.

7 Q. So this is -- these are the thresholds in the ICH
8 guidelines, right?

9 A. Correct.

10 Q. And the lowest threshold -- and, first of all, there
11 are two rows in the chart; the upper row is for drugs for
12 which the maximum daily dose is less than 2 grams a day,
13 right?

14 A. Yes.

15 Q. And tasimelteon is one of those, right?

16 A. Yes.

17 Q. So if we then read across, the first threshold we
18 come to is the 0.05 reporting threshold, right?

19 A. Yes.

20 Q. That means that if you detect an impurity at greater
21 than 0.05 percent, you need to tell the FDA about the
22 existence of the impurity, right?

23 A. Yes.

24 Q. Okay. And then if the impurity -- the next column is
25 the identification threshold. So if you have more than

CROSS-EXAMINATION - DR. BERGMEIER

1 0.1 percent of the impurity or 1 milligram per day of
2 intake, whichever is lower, then you need to not only tell
3 the FDA about the existence of the impurity, but you need to
4 identify the impurity, right?

5 A. Yes.

6 Q. And in this context "identify" means determine the
7 chemical structure of the impurity, right?

8 A. Yes.

9 Q. Okay. And then your reward for identifying the
10 impurity is that you're allowed to have more of it in the
11 drug product, right?

12 A. Yes.

13 Q. And so, you're allowed to have as much as
14 0.15 percent of identified impurities in the drug product,
15 whereas if you don't go to the trouble of identifying the
16 impurity, you need to keep it below 0.1 percent, right?

17 A. You don't have to identify it if you go through the
18 qualification route.

19 Q. Right. Well, let's do it one at a time.

20 So if you -- oh I see what you're saying. If
21 you don't identify it, you can do safety qualification
22 testing on the product rather than going to the trouble of
23 identifying the structure?

24 A. Right, which is what BMS did.

25 Q. But if you go above 0.15 percent for any impurity,

CROSS-EXAMINATION - DR. BERGMEIER

1 even if you identified it, then you have to go through
2 safety qualification testing for the product regardless of
3 whether you've identified it or not, right?

4 A. Yes.

5 Q. So you have a choice, you can -- when you find
6 something that's between 0.1 and 0.15 percent, you can
7 either try to get it under 0.1 percent so you don't have to
8 identify it, right?

9 A. Correct.

10 Q. Or you can identify, in which case you can just leave
11 it alone and you don't have to do the qualification, right?

12 A. Right.

13 Q. Or if you end up going over 0.15 percent, regardless
14 of whether you identify it, you need to do safety tests,
15 right?

16 A. Correct.

17 Q. And safety tests can be quite onerous and expensive,
18 can't they?

19 A. Yes.

20 Q. First of all, you have to figure out how to
21 manufacture the impurity, right?

22 A. Correct.

23 Q. And you need to make large quantities of it, right,
24 for testing?

25 A. Yes.

CROSS-EXAMINATION - DR. BERGMEIER

1 Q. You might have to do animal studies?

2 A. Yes.

3 Q. Those animal studies could go on more many months?

4 A. Yes.

5 Q. They could cost certainly more than a million
6 dollars, maybe multiple millions of dollars, right?

7 A. Perhaps.

8 Q. So there's an incentive not to go over the
9 0.15 percent threshold, right?

10 A. Correct, but one could purify.

11 Q. Yes. When you say "one could purify," you mean one
12 could reduce the amount of the impurity below 0.15 percent?

13 A. Yes.

14 Q. Right. That was my point. I was saying there's an
15 incentive to do that rather than do the qualification safety
16 testing; we agree about that?

17 A. Yes.

18 Q. Now, we can take that down, Mr. Brooks.

19 Highly pure tasimelteon is something that was
20 known in the prior art before the '465 patent, right?

21 A. I think the term "highly pure" is perhaps a little
22 bit subjective, but, yes.

23 Q. Well, one of the items that you discussed on your
24 direct is the Chinese patent application, the CN019
25 application.

CROSS-EXAMINATION - DR. BERGMEIER

1 Do you recall that?

2 A. I believe I discussed the '268, but --

3 Q. Well --

4 THE COURT: He's already said yes and I know
5 about the Chinese patent and the language in the Chinese
6 patent. I can find that it's highly purified. It seems it
7 is not even disputed. Highly purified tasimelteon -- I'm
8 getting tired -- was in the state of the art, I don't think
9 it's disputed; right, it's not disputed?

10 MR. GROOMBRIDGE: Correct.

11 THE COURT: Let's move on. I have a court
12 reporter and it's 5:30.

13 MR. ROZENDAAL: I do think it is important to
14 get the '019 application into evidence.

15 THE COURT: The Chinese application?

16 MR. ROZENDAAL: Yes, Your Honor.

17 THE COURT: I thought it was in evidence.

18 MR. ROZENDAAL: Well, there are two; one is in
19 and one I'm about to put in it.

20 MR. GROOMBRIDGE: For clarity for the Court, one
21 is the subject, is the obviousness reference is one called
22 '268. This is a different one and we may be hearing about
23 how they are or aren't connected.

24 THE COURT: Okay. Sorry.

25 Can they move it into evidence without

CROSS-EXAMINATION - DR. BERGMEIER

1 objection?

2 MR. GROOMBRIDGE: They can, Your Honor, without
3 objection.

4 THE COURT: All right. You can bring it in
5 without objection. It's admitted.

6 What exhibit is it?

7 MR. ROZENDAAL: It's Exhibit DTX-411.

8 THE COURT: Okay.

9 (DTX-411 was admitted.)

10 MR. ROZENDAAL: And we can pull it up, please,
11 Mr. Brooks.

12 BY MR. ROZENDAAL:

13 Q. And just so that we're clear, if we go to -- oh, I'm
14 sorry.

15 If we go to DTX-411.53, which is the last page
16 of the document and we focus on the bottom part of the first
17 paragraph, please. We'll see that if we start with the line
18 that begins with "Eluent was taken and the solvent was
19 removed to obtain 2.2 grams of white needle-like crystal
20 tasimelteon with a purity of 99.9 percent and a yield of
21 92 percent."

22 And so we agree, don't we, that this is a
23 reference that discloses 99.9 percent pure tasimelteon,
24 right?

25 A. They do state that it is 99.9 percent pure.

CROSS-EXAMINATION - DR. BERGMEIER

1 Q. All right. And if it is 99.9 percent pure, then we
2 also agree that the level of impurities of -- the level of
3 each Impurities 1 through 3, 5 and 6 would necessarily have
4 been less than 0.15 percent, right?

5 A. Yes.

6 Q. Okay. And so, this example from the '019 patent
7 application, which, for the record, was published on
8 May 8th, 2013, was -- pardon me. This embodiment with the
9 99.9 percent purity satisfies all purity limitations of
10 Claim 10 of the '465 patent, right?

11 A. What do you mean "satisfies all limitations?"

12 Q. Well, I mean that if I made this product, which is
13 described here, and it's 99.9 percent pure, then that
14 would -- that would have less than 0.15 percent of all of
15 the impurities listed in -- of each of the impurities listed
16 in the '465 patent?

17 A. I think it probably would. I have my doubts as to
18 the 99.9 percent purity.

19 Q. Okay. So you think that the reference is not
20 accurately describing the purity?

21 A. No.

22 Q. Okay. But if it were accurately describing the
23 purity, then there wouldn't be any individual impurity
24 greater than 0.15 percent, right?

25 A. That would be hard to do.

CROSS-EXAMINATION - DR. BERGMEIER

1 Q. Right. So that's -- so we agree that it -- none of
2 them would be over that threshold, right?

3 A. Yes.

4 Q. Okay. Now, in the interest of trying to speed this
5 up for time -- you can take that down, Mr. Brooks.

6 We agree, there's another Chinese application,
7 right, it's the '268 Chinese application, that's the one
8 that we've talked about before in this case?

9 A. Yes.

10 Q. And that one, on your reading of the claim, actually
11 uses even the claimed process of Claim 10 of the '465
12 patent, right?

13 A. Yes.

14 Q. So it goes through the route of a carboxamide, which
15 is reduced to a methanamine, which is then propionylated to
16 make tasimelteon, right?

17 A. Yes.

18 Q. Yes, it's reduced and reacted with acid. Pardon me,
19 the carboxamide is reduced and reacted with acid to make the
20 methanamine --

21 THE COURT: I think you need to start over,
22 because this seems to me to be a very central point about
23 whether it's sequential or it is a unified process.

24 BY MR. ROZENDAAL:

25 Q. Okay. So I'm now asking you to apply your

1 interpretation of the claim, okay, Doctor.

2 So as you interpret the claim, the CN268 patent
3 carries out both of the process steps that are described at
4 the beginning of Claim 1 and, therefore, also Claim 10 of
5 the '465 patent, right?

6 A. I believe that's correct.

7 Q. Okay. Well, I think it's important that we be sure.
8 So if there's any doubt about it --

9 A. If I could take a look at the language of that one.

10 Q. That would be DTX-301. It's in your binder and it's
11 also in evidence.

12 THE COURT: So let's do this, we have already
13 gone about half an hour. Why don't we call it a day and
14 resume tomorrow.

15 All right. You can step down.

16 Are there any issues I need to attend to
17 tonight?

18 MR. GROOMBRIDGE: None that we're aware of, Your
19 Honor.

20 MR. ROZENDAAL: No, Your Honor.

21 THE COURT: And then you need to be -- we're
22 going to finish up, I would assume, before lunch, certainly
23 I would expect, and then we're doing claim construction,
24 right?

25 MR. ROZENDAAL: Yes.

1 THE COURT: I mean, we were going to get to it
2 today, but it took a lot longer.

3 MR. GROOMBRIDGE: That makes sense to us, Your
4 Honor. Let's get to it.

5 THE COURT: Okay. And then you'll be prepared
6 for -- and we'll debate about what and how long closing
7 arguments Friday morning.

8 All right, okay, that's the plan right now.
9 Subject to change, but that's the plan.

10 Okay. And we're going to break for the evening.
11 Thanks.

12 MR. ROZENDAAL: Oh, may the witness be
13 admonished not to --

14 THE COURT: Oh, yeah, that is the one downside,
15 but this the way we were. So the witness is not to engage
16 in any substantive conversations.

17 So just enjoy your dinner. Speak about the
18 dinner, don't speak about the case.

19 All right. I have to reboot my computer; you're
20 all free.

21 (Whereupon, the following proceeding concluded
22 at 5:36 p.m.)

23 I hereby certify the foregoing is a true
24 and accurate transcript from my stenographic notes in the
25 proceeding.

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/s/ Michele L. Rolfe, RPR, CRR
U.S. District Court

	815:8, 817:18, 819:18	801:18, 803:14, 804:9, 804:19, 805:7, 807:13, 809:14, 816:12, 817:12, 821:13, 822:18, 836:1, 836:23, 836:25, 837:9, 858:3, 858:9, 859:5, 859:8, 861:8, 863:19, 867:10, 871:12, 942:12, 943:12, 950:24, 951:16, 953:12, 953:17, 953:19, 960:7, 960:8, 962:23, 962:24, 963:16, 966:6, 966:12, 967:12, 968:1, 968:2, 968:5, 968:8, 972:8, 972:24, 974:7, 974:10, 976:17, 977:22, 978:6, 978:23, 979:7, 979:21, 981:25, 987:19, 992:17, 993:8, 995:2, 1000:4, 1002:5	102(a) [11] - 764:11, 764:13, 764:16, 764:22, 764:25, 765:2, 765:6, 766:2, 766:7, 766:9, 766:11	19 [5] - 876:23, 885:4, 974:10, 977:24
'019 [4] - 973:9, 974:13, 998:15, 1000:7	'704 [1] - 761:13	1.. [1] - 952:12		1980s [1] - 712:16
'244 [42] - 727:9, 727:15, 727:23, 728:4, 800:15, 800:17, 803:11, 803:15, 805:6, 805:15, 805:22, 806:5, 806:15, 806:23, 807:11, 807:23, 808:10, 809:18, 810:8, 811:4, 811:20, 813:11, 813:21, 814:5, 814:7, 815:2, 818:25, 819:2, 820:1, 820:3, 820:17, 820:18, 822:12, 822:13, 823:25, 824:4, 824:5, 827:13, 876:5, 876:11, 882:21, 883:1	'80s [1] - 838:6	1.1 [1] - 805:1		1983 [2] - 712:16, 838:24
'268 [3] - 998:3, 998:23, 1001:8	'829 [9] - 704:22, 705:1, 818:21, 818:23, 819:3, 819:17, 880:24, 882:2, 882:3	1.43 [1] - 921:8		1988 [3] - 900:6, 900:12, 901:2
'465 [23] - 680:18, 687:18, 687:19, 761:13, 943:12, 950:17, 953:2, 954:2, 954:12, 959:9, 972:7, 973:4, 980:4, 982:5, 982:13, 982:15, 991:7, 993:7, 997:21, 1000:11, 1000:17, 1001:12, 1002:6	'90s [1] - 838:6	1/31/2020 [1] - 786:4		1991 [4] - 849:23, 902:11, 902:20, 929:6
'468 [1] - 979:16	'910 [8] - 704:22, 705:1, 820:12, 820:15, 820:21, 821:2, 821:10, 821:21	10 [38] - 723:5, 728:25, 807:2, 845:13, 851:18, 853:2, 853:4, 866:23, 870:5, 876:17, 881:6, 893:5, 910:8, 924:3, 924:4, 927:3, 928:14, 928:21, 929:20, 948:4, 953:2, 954:1, 954:2, 956:9, 956:17, 957:7, 960:4, 960:5, 962:12, 962:17, 962:22, 963:12, 970:8, 972:22, 980:4, 1000:11, 1001:12, 1002:5	102(b) [5] - 764:7, 764:10, 764:23, 765:10, 765:12	1992 [1] - 896:10
'487 [10] - 705:6, 822:7, 822:10, 822:17, 822:22, 824:6, 824:20, 826:7, 826:10, 828:17	'924 [1] - 799:8	100 [10] - 728:25, 807:2, 866:24, 870:6, 870:18, 871:25, 875:9, 875:17, 876:18, 884:18	102(b) [4] - 764:23, 765:8, 766:12, 776:2	1995 [3] - 713:4, 920:12, 929:7
'510 [1] - 761:13	'977 [2] - 982:12, 982:13	100-milligram [4] - 729:3, 876:15, 877:11, 884:6	10:00 [3] - 738:13, 902:23, 915:14	1997 [3] - 896:11, 929:7
'511 [1] - 761:13	/		11 [1] - 963:12	1:00 [5] - 913:2, 913:5, 913:10, 913:15, 916:10
'529 [15] - 953:3, 953:5, 953:11, 960:18, 960:20, 973:7, 974:14, 974:21, 975:24, 976:5, 976:13, 976:15, 977:25, 978:3, 978:10	/s [1] - 1004:2		11.1.2.1 [2] - 876:22, 883:25	1st [1] - 934:18
'604 [8] - 704:22, 803:10, 804:9, 811:25, 813:12	0		11:00 [1] - 901:14	
	0.05 [5] - 921:7, 921:12, 924:3, 994:19, 994:22		11:15 [1] - 776:22	2 [38] - 710:2, 710:3, 728:19, 729:9, 758:21, 799:5, 801:18, 806:3, 808:21, 817:10, 858:3, 858:10, 859:4, 859:8, 864:10, 867:11, 873:23, 884:25, 885:12, 928:25, 950:24, 951:16, 953:17, 953:19, 959:11, 959:22, 961:17, 965:25, 966:6, 966:12, 968:8, 972:8, 972:24, 978:6, 978:23, 979:21, 981:25, 994:13
	0.05-milligram [1] - 910:1		12 [6] - 794:13, 795:15, 846:13, 913:16, 964:5, 994:3	2.2 [1] - 999:20
	0.1 [4] - 995:2, 995:17, 996:7, 996:8		12-hour [1] - 913:23	2.4 [1] - 961:20
	0.1 [1] - 983:7		12/27/2019 [2] - 739:2, 749:14	2.5 [1] - 963:2
	0.15 [9] - 993:5, 995:15, 996:1, 996:14, 997:10, 997:13, 1000:5, 1000:15, 1000:25		12:26 [1] - 936:22	20 [47] - 703:9, 727:21, 728:3, 728:25, 729:10, 746:5, 773:2, 773:5, 773:10, 788:24, 797:5, 799:12, 806:13, 806:20, 807:4, 807:5, 812:19, 816:7, 816:15, 819:10, 823:2, 845:9, 846:9, 853:3, 853:4, 858:19, 866:23, 870:5, 871:7, 873:13, 874:21, 875:4, 882:22,
	0.2 [1] - 923:14		13 [3] - 738:24, 790:20, 819:4	
	0.3 [1] - 910:9		1347 [1] - 751:24	
	0.5 [17] - 719:18, 719:22, 723:4, 808:14, 837:13, 852:23, 852:25, 871:17, 909:25, 910:9, 911:17, 928:13, 928:20, 930:8, 930:14, 934:1, 996:7		1355 [2] - 751:25, 752:13	
	0.5-milligram [3] - 906:16, 909:25, 929:24		1358 [2] - 752:16, 753:5	
	01163032 [3] - 785:12, 789:16, 789:17		1359 [1] - 752:16	
	1		13th [4] - 740:24, 779:22, 780:5, 787:12	
	1 [65] - 680:22, 681:5, 682:16, 710:2, 710:3, 724:22,		14 [8] - 724:25, 725:3, 725:4, 818:23, 819:3, 819:6, 819:17, 973:3	
			15 [20] - 739:4, 742:21, 745:14, 748:1, 748:14, 749:6, 750:10, 754:20, 754:24, 754:25, 758:20, 759:21, 760:9, 771:18, 776:20, 776:22, 789:20, 794:5, 795:12, 972:23	
			15th [12] - 733:9, 740:18, 740:25, 745:24, 747:13, 748:21, 749:19, 754:15, 755:19, 756:1, 780:7, 791:12	
			17 [2] - 839:1, 976:11	
			18 [6] - 741:1, 795:12, 846:13, 876:20, 976:24, 977:2	
			18-651-CFC [1] - 1:6	

883:3, 883:8, 883:12, 883:13, 883:18, 910:5, 910:8, 910:14, 911:22, 912:3, 923:15, 923:19, 924:6, 984:11 20-milligram [8] - 812:13, 812:15, 816:13, 818:10, 821:5, 885:19, 885:22, 911:15 20-milligram-per-day [1] - 808:17 2000 [21] - 714:6, 714:17, 715:17, 718:8, 897:11, 899:17, 903:8, 919:13, 919:14, 919:23, 925:17, 926:16, 929:2, 929:17, 929:21, 932:21, 932:23, 933:12, 935:11, 957:11 2001 [3] - 716:13, 929:25, 930:17 2002 [3] - 716:19, 842:9, 852:18 2003 [4] - 719:15, 725:22, 855:3, 919:14 2004 [4] - 716:25, 947:11, 947:13, 959:8 2005 [2] - 717:7, 916:9 2007 [4] - 720:10, 727:8, 917:19, 918:13 2009 [5] - 728:14, 730:2, 730:11, 865:4, 872:20 2010 [73] - 721:14, 733:9, 735:23, 738:24, 740:18, 740:19, 740:25, 741:11, 742:21, 745:14, 745:24, 746:4, 746:18, 747:2, 747:14, 748:1, 748:14, 748:21, 749:6, 749:19, 750:10, 754:11, 754:15, 754:20, 754:24, 754:25, 755:19, 756:2, 759:21, 760:10, 765:11, 767:23, 767:24, 767:25, 768:4, 769:4, 769:5, 770:3, 771:18, 772:17, 773:14, 776:15, 779:22, 780:2, 780:5, 780:7, 780:23, 781:4, 782:9, 785:10, 787:12, 787:19, 788:24, 789:14, 789:21, 789:24, 790:2, 790:5, 790:9, 790:20, 791:9, 791:12, 792:19, 794:5, 795:12, 796:25, 816:10, 816:15, 816:25, 860:4, 860:12, 863:23 2011 [23] - 742:25, 744:11, 760:12, 762:3, 762:13, 763:14, 763:20, 763:22, 764:1, 765:18, 765:19, 767:5, 767:7, 767:9, 767:16, 768:10, 768:23, 776:11, 798:14, 878:14, 893:22, 966:4 2012 [16] - 705:11, 705:24, 708:16, 709:18, 722:23, 809:23, 832:15, 859:11, 881:13, 883:6, 910:13, 934:18, 934:22, 935:5, 936:7, 936:13 2013 [3] - 739:4, 757:24, 1000:9 2013/0197076 [1] - 827:1 2014 [3] - 675:24, 684:22, 739:4 2015 [21] - 746:3, 746:16, 746:20, 748:19, 749:21, 754:18, 755:24, 757:16, 757:22, 759:21, 762:13, 779:7, 780:16, 781:7, 781:9, 792:15, 792:18, 792:25, 793:6, 797:21, 919:1 2017 [2] - 829:25, 845:8 2018 [1] - 751:25 2019 [3] - 747:17, 747:21, 749:10 2020 [2] - 736:7, 740:24 2021 [3] - 759:1, 761:11, 770:23 2022 [2] - 1:14, 858:15 21 [1] - 739:4 214778 [1] - 725:23 23 [6] - 767:7, 767:9, 767:15, 882:13, 974:11, 979:13 23rd [3] - 763:14, 768:23 24 [13] - 706:9, 708:3, 741:23, 847:4, 869:20, 914:16, 941:20, 962:10, 962:13, 962:14, 962:16, 967:1, 974:11 24-hour [12] - 707:23, 708:2, 712:18, 714:22, 715:23, 773:19, 804:16, 805:19, 806:1, 814:24, 870:13, 905:17 24.36 [2] - 921:14, 921:18 24.45 [1] - 909:2 24.69 [1] - 922:14 24.7 [1] - 922:9 24.9-hour [1] - 922:15 25 [5] - 808:19, 867:2, 870:8, 877:2, 981:23 25.1 [1] - 922:4 25.43 [3] - 921:23, 921:25, 922:12 26 [3] - 678:8, 697:5, 808:19 26th [1] - 780:23 27th [2] - 749:10, 781:4 283 [2] - 850:5, 850:8 29 [4] - 932:18, 933:8, 933:12, 969:14 29th [1] - 941:4 2nd [2] - 780:2, 791:9	806:18, 807:15, 809:4, 809:19, 810:1, 810:24, 811:6, 811:11, 811:16, 813:12, 815:13, 817:18, 819:7, 819:16, 819:18, 820:22, 821:11, 821:20, 821:22, 822:15, 822:21, 822:23, 823:3, 826:21, 837:13, 855:10, 861:7, 878:3, 878:18, 878:24, 885:3, 885:12, 906:19, 910:5, 931:24, 931:25, 950:24, 951:16, 953:12, 953:17, 953:19, 959:21, 961:17, 966:6, 966:12, 967:13, 968:1, 968:3, 968:5, 968:12, 972:9, 972:24, 976:17, 977:22, 978:6, 978:23, 979:7, 979:21, 981:25, 987:20, 992:8, 992:17, 993:8, 1000:4 3-hour [1] - 864:10 30 [17] - 1:14, 702:12, 702:14, 708:4, 708:8, 709:8, 709:12, 759:1, 808:2, 808:13, 813:5, 823:14, 823:16, 824:1, 887:24, 932:18, 932:23 30,000 [1] - 682:25 30th [1] - 738:13 31 [2] - 933:8, 933:12 31st [2] - 736:7, 754:19 36 [1] - 921:17 36-hour [1] - 921:7 38 [1] - 974:11 39 [1] - 932:20 3:15 [1] - 895:10	835:20, 863:3, 906:19 40 [1] - 846:9 402 [2] - 732:9, 738:5 41.25 [1] - 805:16 411 [1] - 885:3 419.3 [2] - 746:5, 746:10 419.4 [1] - 746:6 42 [5] - 771:7, 793:17, 795:20, 795:22, 798:1 42.9 [
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<p>50 [11] - 727:21, 728:3, 728:25, 846:13, 866:24, 870:6, 873:13, 874:21, 875:4, 882:22, 893:7</p> <p>50-milligram [1] - 812:19</p> <p>54 [2] - 969:14, 990:20</p> <p>55 [2] - 830:15, 924:4</p> <p>59 [1] - 846:16</p> <p>5:00 [2] - 916:10, 923:16</p> <p>5:30 [1] - 998:13</p> <p>5:36 [1] - 1003:23</p> <p>5th [1] - 935:5</p>	<p style="text-align: center;">8</p> <p>8 [8] - 815:6, 845:16, 846:9, 866:11, 874:19, 961:25, 967:17</p> <p>8.10 [1] - 907:10</p> <p>8.11 [1] - 908:2</p> <p>8.12 [1] - 909:17</p> <p>8.15 [1] - 911:8</p> <p>8.17 [1] - 913:9</p> <p>8.3 [2] - 899:14</p> <p>8.6 [1] - 902:18</p> <p>8.7 [1] - 903:17</p> <p>80 [1] - 739:9</p> <p>84 [9] - 736:6, 739:10, 739:11, 742:5, 785:8, 786:3, 788:16, 788:20, 788:22</p> <p>895 [1] - 751:24</p> <p>8:30 [1] - 672:4</p> <p>8th [1] - 1000:9</p>	<p>ability [10] - 722:8, 832:23, 849:1, 851:10, 889:19, 897:2, 922:24, 922:25, 929:11, 933:5</p> <p>able [37] - 713:21, 718:9, 718:10, 729:15, 742:11, 771:3, 771:10, 772:11, 798:3, 833:8, 849:7, 851:12, 851:15, 851:25, 852:1, 871:9, 895:6, 902:23, 904:22, 905:1, 906:21, 907:2, 921:5, 921:13, 921:14, 922:16, 961:10, 977:12, 982:22, 982:23, 983:3, 983:5, 983:9, 983:15, 983:18, 983:19, 983:23</p> <p>abnormality [1] - 931:15</p> <p>abolish [1] - 914:8</p> <p>abolishing [1] - 912:8</p> <p>absent [1] - 733:4</p> <p>absolute [1] - 858:25</p> <p>absolutely [1] - 757:8</p> <p>abstract [8] - 726:6, 830:15, 860:2, 925:19, 926:21, 927:8, 928:12, 931:4</p> <p>ACA [1] - 753:23</p> <p>academic [2] - 701:15, 888:4</p> <p>Academy [6] - 702:4, 702:6, 702:23, 703:11, 723:2, 723:17</p> <p>accept [4] - 680:22, 767:10, 800:20, 817:22</p> <p>accepted [2] - 710:24, 839:6</p> <p>access [5] - 681:11, 786:13, 797:20, 798:4, 886:1</p> <p>accessed [5] - 747:17, 747:21, 757:8, 797:22, 798:2</p> <p>accidentally [1] - 905:6</p> <p>accomplish [1] - 771:4</p> <p>according [6] - 689:24, 711:8,</p>	<p>763:24, 878:13, 916:19, 974:20</p> <p>accuracy [1] - 749:2</p> <p>accurate [7] - 699:18, 748:20, 762:23, 830:18, 831:2, 836:6, 1003:25</p> <p>accurately [4] - 790:8, 795:16, 1000:21, 1000:23</p> <p>achieve [8] - 804:3, 805:11, 810:6, 841:7, 852:4, 853:15, 912:7, 915:19</p> <p>achieved [7] - 709:16, 762:24, 871:16, 914:7, 921:6, 921:7, 929:13</p> <p>achieving [1] - 862:20</p> <p>acid [3] - 962:11, 1001:19, 1001:20</p> <p>acknowledge [2] - 935:9, 937:6</p> <p>acknowledgments [1] - 926:4</p> <p>acronym [1] - 867:6</p> <p>act [2] - 831:12, 848:13</p> <p>acting [3] - 726:8, 810:9, 812:4</p> <p>ACTION [1] - 1:5</p> <p>action [1] - 810:12</p> <p>actions [1] - 861:3</p> <p>active [1] - 843:2</p> <p>activities [2] - 849:2, 863:11</p> <p>activity [1] - 727:18</p> <p>actual [5] - 707:9, 824:18, 866:6, 877:6, 921:25</p> <p>add [5] - 819:17, 821:21, 823:3, 943:2, 972:1</p> <p>added [1] - 966:8</p> <p>addition [3] - 748:25, 769:17, 848:13</p> <p>additional [9] - 769:15, 807:15, 819:23, 820:4, 820:7, 822:3, 823:7, 906:19, 977:19</p> <p>Additional [2] - 758:8, 758:11</p> <p>address [5] - 693:21, 872:25, 938:10, 939:14, 981:14</p> <p>addressed [2] - 785:16, 894:7</p> <p>addressing [2] -</p>	<p>752:6, 807:18</p> <p>adds [2] - 819:19, 823:5</p> <p>adduce [3] - 770:17, 770:18, 790:7</p> <p>adducement [1] - 737:23</p> <p>adequate [2] - 981:9, 981:13</p> <p>adjudicate [1] - 751:11</p> <p>adjudicating [1] - 751:10</p> <p>adjust [4] - 991:22, 992:1, 992:19, 992:22</p> <p>adjusting [1] - 992:9</p> <p>administer [5] - 715:22, 773:5, 788:24, 820:6, 825:10</p> <p>administered [18] - 727:21, 727:25, 728:2, 808:2, 817:2, 821:12, 823:8, 823:16, 823:20, 823:21, 823:22, 827:20, 827:21, 830:20, 836:9, 837:13, 841:8, 841:12</p> <p>administering [25] - 710:5, 710:6, 714:19, 718:2, 719:21, 773:2, 806:13, 807:1, 807:4, 808:13, 812:25, 816:7, 816:23, 818:12, 823:1, 823:5, 824:1, 824:21, 824:22, 825:9, 825:24, 826:1, 826:16, 827:16, 876:17</p> <p>administers [3] - 912:25, 913:5, 916:22</p> <p>administration [18] - 723:8, 797:3, 797:5, 807:18, 807:25, 808:11, 813:5, 821:9, 836:5, 837:18, 879:17, 879:19, 880:4, 923:7, 925:22, 927:8, 931:6, 931:9</p> <p>Administration [1] - 850:16</p> <p>admissibility [7] - 737:4, 737:9,</p>
<p style="text-align: center;">6</p> <p>6 [30] - 789:4, 805:4, 806:10, 813:7, 843:20, 855:8, 919:12, 950:25, 951:17, 953:12, 953:17, 953:19, 966:7, 966:12, 968:3, 968:5, 968:12, 972:8, 972:24, 976:17, 977:22, 978:6, 978:23, 979:7, 979:21, 981:25, 987:20, 992:17, 993:9, 1000:4</p> <p>6.6 [1] - 804:25</p> <p>6.64 [1] - 855:20</p> <p>62 [2] - 941:20, 941:24</p>	<p style="text-align: center;">9</p> <p>9 [12] - 779:13, 794:13, 795:15, 802:3, 804:23, 805:2, 847:19, 855:25, 880:21, 963:1, 968:3, 984:22</p> <p>9-hour [1] - 802:17</p> <p>90 [1] - 898:9</p> <p>901 [3] - 748:9, 749:13, 796:19</p> <p>902 [2] - 749:7, 749:12</p> <p>902(b)(2) [1] - 749:1</p> <p>92 [1] - 999:22</p> <p>93 [1] - 873:10</p> <p>99.6 [1] - 978:19</p> <p>99.9 [8] - 680:6, 999:21, 999:24, 1000:1, 1000:2, 1000:10, 1000:14, 1000:19</p> <p>9:00 [6] - 904:20, 906:17, 913:1, 914:22, 916:5, 920:1</p> <p>9th [1] - 893:22</p>			
<p style="text-align: center;">7</p> <p>7 [22] - 763:22, 764:1, 778:20, 802:3, 802:17, 804:22, 805:2, 812:21, 815:6, 855:24, 866:8, 866:11, 873:1, 880:21, 884:13, 942:14, 965:24, 967:6, 974:7, 987:24, 988:8, 988:25</p> <p>70 [7] - 830:16, 942:15, 943:6, 943:10, 946:4, 952:3, 952:10</p> <p>71 [2] - 946:4, 952:3</p> <p>72 [4] - 942:22, 943:7, 946:5, 952:3</p> <p>73.9 [1] - 984:22</p> <p>7th [2] - 742:25, 767:5</p>	<p style="text-align: center;">A</p> <p>a.m [5] - 672:4, 913:2, 913:5, 915:14, 916:10</p> <p>abbreviated [2] - 710:3, 867:25</p> <p>abbreviation [1] - 912:9</p>			

<p>737:13, 750:1, 758:13, 770:20, 948:14 admissible [1] - 789:25 admission [1] - 794:21 admissions [1] - 939:11 admit [6] - 697:4, 790:14, 795:22, 796:4, 829:22, 949:5 admitted [64] - 690:21, 697:7, 699:3, 699:6, 713:11, 713:12, 714:13, 714:14, 715:13, 715:14, 717:14, 717:15, 717:16, 717:17, 717:18, 719:11, 719:12, 720:17, 720:18, 721:21, 721:22, 724:1, 724:2, 724:12, 725:18, 725:19, 727:2, 727:3, 730:8, 730:9, 738:6, 749:12, 798:21, 798:22, 828:21, 828:23, 830:7, 830:8, 850:7, 850:8, 901:7, 901:8, 902:15, 902:16, 911:6, 911:7, 919:8, 919:9, 958:5, 958:7, 958:23, 965:21, 965:22, 966:16, 974:3, 974:4, 975:14, 975:15, 980:24, 980:25, 984:6, 984:8, 999:6, 999:10 admonished [1] - 1003:14 advance [30] - 690:25, 729:12, 841:15, 850:18, 850:24, 851:3, 851:7, 852:3, 864:10, 885:7, 885:10, 885:13, 902:24, 903:2, 905:7, 905:10, 912:7, 913:3, 913:18, 913:21, 913:22, 914:4, 914:7, 914:8, 914:15, 917:1, 920:21, 932:3, 933:5 advanced [4] - 843:15, 904:24, 906:20,</p>	<p>954:17 Advances [1] - 850:17 advances [3] - 836:10, 843:5, 851:25 advancing [1] - 927:18 advantage [1] - 849:9 advised [1] - 828:16 advisory [2] - 829:20, 829:23 affect [2] - 684:6, 838:3 affects [1] - 841:9 affidavit [3] - 762:20, 765:17, 767:5 affiliate [1] - 701:16 affinities [3] - 858:22, 859:1 affinity [1] - 799:19 affirmed [1] - 895:21 afternoon [8] - 793:16, 829:1, 829:2, 836:9, 895:25, 924:24, 984:15, 984:16 afterwards [2] - 883:17, 958:25 agent [5] - 709:2, 709:4, 709:10, 710:7, 843:1 aggregate [1] - 684:4 ago [2] - 702:14, 887:24 agomelatine [8] - 861:21, 862:5, 862:9, 862:16, 862:18, 862:25, 863:10, 864:8 Agomelatine's [1] - 863:7 agonist [13] - 722:1, 722:3, 724:8, 812:4, 814:20, 830:21, 831:6, 831:9, 832:6, 832:10, 862:10, 865:20, 965:4 agonists [8] - 722:6, 722:12, 860:15, 860:23, 861:2, 861:19, 863:24, 873:20 agree [55] - 688:16, 689:11, 696:20, 710:21, 737:14, 761:10, 774:14, 838:1, 840:9, 840:13, 851:10, 851:14, 852:2, 856:9, 856:10, 857:5, 857:13,</p>	<p>858:13, 860:21, 860:24, 861:1, 862:18, 871:12, 872:23, 876:10, 876:13, 881:12, 882:1, 882:5, 915:7, 944:13, 944:17, 946:7, 950:15, 950:18, 951:20, 953:1, 953:4, 954:18, 955:4, 955:14, 976:15, 978:14, 978:18, 979:6, 979:8, 985:9, 985:16, 990:25, 991:21, 997:17, 999:23, 1000:3, 1001:2, 1001:7 agreed [7] - 700:14, 711:19, 766:23, 860:13, 884:17, 898:18, 947:18 agreeing [1] - 944:12 agreement [6] - 672:10, 894:16, 946:10, 949:9, 949:15, 952:7 agrees [4] - 673:3, 944:7, 944:8, 947:16 ahead [18] - 675:6, 696:10, 700:10, 747:15, 753:21, 777:11, 784:22, 796:6, 833:20, 889:9, 914:17, 917:2, 956:22, 977:11, 984:12, 985:22, 986:3, 994:1 air [1] - 890:14 Al [5] - 715:21, 842:9, 842:10, 887:7, 962:11 al [8] - 1:8, 716:11, 716:19, 716:25, 717:6, 721:14, 935:11 alerting [1] - 708:24 alertness [2] - 830:24, 832:18 Alfred [2] - 702:17, 887:2 alive [1] - 888:15 allege [1] - 946:9 alleged [2] - 761:15, 761:17 allegedly [1] - 801:10 alleges [3] - 943:11, 944:5, 952:10 allow [6] - 737:23, 797:18, 797:24,</p>	<p>798:3, 848:8, 949:20 allowed [7] - 696:2, 798:8, 974:25, 976:9, 993:14, 995:11, 995:14 allowing [1] - 967:11 alludes [1] - 726:3 almost [2] - 882:6, 882:7 alone [3] - 953:12, 978:5, 996:12 alternatively [1] - 955:2 aluminum [1] - 964:4 Ambarish [1] - 958:12 ambiguous [1] - 689:6 amendment [3] - 967:20, 969:7, 969:15 American [7] - 702:3, 702:4, 702:6, 702:23, 703:11, 723:2, 723:17 Amneal [1] - 751:24 amnesic [1] - 891:24 amount [9] - 745:10, 753:24, 753:25, 843:11, 843:14, 923:3, 978:22, 993:13, 997:13 amounts [2] - 875:12, 953:19 analogy [1] - 849:7 analysis [5] - 790:22, 904:11, 935:20, 968:9, 990:16 analytical [1] - 693:8 analyze [2] - 703:15, 983:22 analyzed [2] - 705:5, 991:8 analyzing [5] - 677:12, 801:17, 819:3, 822:17, 955:10 AND [1] - 1:3 and.. [1] - 968:18 animal [3] - 726:5, 997:2, 997:4 animals [4] - 712:17, 726:4, 840:11, 890:5 annotations [1] - 965:25 annual [1] - 936:13 ANOVA [1] - 877:14 answer [12] - 672:15, 677:20, 685:22, 697:13, 699:10, 786:11, 810:21, 834:1, 862:13, 900:1, 956:22,</p>	<p>991:19 answers [1] - 900:2 anticipate [3] - 773:15, 816:3, 818:5 anticipated [5] - 800:21, 815:19, 815:21, 948:23, 975:23 anticipates [1] - 773:24 anticipation [5] - 680:9, 681:8, 772:24, 815:9, 815:10 anticipatory [1] - 816:2 antidepressants [1] - 862:12 anyway [3] - 688:20, 894:12, 895:8 apart [2] - 692:17, 693:16 apologies [1] - 759:24 apologize [7] - 751:12, 752:14, 753:1, 797:10, 833:22, 872:5, 882:15 Apotex [7] - 671:18, 683:18, 980:9, 983:12, 983:14, 983:18, 992:7 appeal [2] - 753:10, 796:13 appear [3] - 722:12, 908:4, 939:6 APPEARANCES [1] - 671:1 appended [4] - 746:22, 766:8, 768:8, 768:25 applicant [1] - 727:5 Application [1] - 826:25 application [22] - 726:19, 726:20, 727:5, 795:19, 827:4, 876:5, 876:11, 876:14, 953:6, 953:16, 974:21, 979:18, 980:1, 980:17, 982:11, 997:25, 998:1, 998:15, 998:16, 1000:8, 1001:7, 1001:8 applications [2] - 862:3, 862:4 applied [1] - 956:3 apply [4] - 770:17,</p>
---	---	--	--	---

<p>803:9, 833:10, 1002:1</p> <p>appreciate [2] - 774:9, 951:17</p> <p>Approach [1] - 959:13</p> <p>approach [4] - 736:2, 777:9, 924:20, 977:5</p> <p>approaches [1] - 959:20</p> <p>appropriate [3] - 814:23, 924:2, 924:10</p> <p>appropriately [2] - 930:8, 932:2</p> <p>approvable [1] - 685:4</p> <p>approval [4] - 687:20, 740:5, 757:25, 829:21</p> <p>approved [3] - 685:1, 687:17, 736:12</p> <p>approximate [1] - 869:18</p> <p>aqua [2] - 979:1, 979:2</p> <p>arbitrate [1] - 775:14</p> <p>archive [1] - 735:5</p> <p>archive's [1] - 762:24</p> <p>area [2] - 807:3, 890:8</p> <p>areas [1] - 896:25</p> <p>Arendt [16] - 713:3, 713:15, 713:18, 720:9, 896:15, 896:16, 896:19, 900:8, 901:2, 901:12, 903:25, 917:15, 919:22, 920:10, 929:7, 930:23</p> <p>ARENDR [1] - 896:17</p> <p>argue [1] - 738:4</p> <p>argued [4] - 685:10, 685:12, 685:18, 938:22</p> <p>arguing [3] - 686:15, 698:12, 764:10</p> <p>argument [17] - 673:1, 675:8, 678:8, 686:9, 687:9, 688:13, 689:2, 698:3, 699:5, 738:5, 738:13, 772:23, 774:14, 774:15, 774:22, 800:20, 947:20</p> <p>arguments [2] - 941:21, 1003:8</p> <p>arise [1] - 802:24</p> <p>arm [1] - 797:4</p> <p>arms [1] - 816:19</p> <p>Arms [2] - 791:25, 792:2</p> <p>arose [1] - 938:16</p>	<p>arrange [1] - 785:15</p> <p>arrive [2] - 809:25, 813:15</p> <p>arriving [2] - 810:24, 814:10</p> <p>ARSH [1] - 671:12</p> <p>art [129] - 673:14, 673:25, 676:1, 676:24, 678:17, 679:7, 680:8, 680:13, 681:9, 695:12, 697:16, 701:9, 705:11, 705:18, 705:20, 705:24, 709:23, 710:17, 710:23, 711:3, 722:21, 729:4, 732:11, 732:16, 732:23, 733:1, 734:18, 734:25, 735:18, 737:11, 737:17, 743:2, 743:16, 750:7, 750:8, 750:16, 750:17, 751:9, 754:7, 757:3, 759:12, 759:15, 759:19, 760:17, 760:20, 761:22, 764:7, 764:10, 764:11, 764:13, 764:16, 764:23, 764:24, 764:25, 765:6, 765:12, 766:9, 771:10, 795:3, 801:3, 801:4, 801:6, 801:10, 802:6, 802:8, 802:21, 803:8, 807:20, 808:22, 809:23, 810:23, 811:13, 811:19, 813:14, 814:9, 815:22, 819:13, 819:24, 821:17, 833:8, 849:13, 860:12, 863:23, 879:6, 879:8, 881:23, 882:3, 883:6, 891:12, 891:13, 898:15, 910:12, 915:23, 917:8, 917:9, 919:18, 922:23, 923:6, 923:18, 924:1, 938:12, 938:20, 938:23, 938:24, 939:1, 939:17, 940:2, 940:4, 940:7,</p>	<p>941:22, 942:1, 942:2, 942:3, 944:13, 944:17, 953:24, 954:4, 954:9, 954:12, 955:9, 955:12, 956:1, 991:6, 991:21, 992:11, 993:7, 997:21, 998:9</p> <p>art's [1] - 811:8</p> <p>article [85] - 678:25, 679:14, 679:15, 679:17, 679:19, 679:24, 679:25, 689:24, 698:6, 698:16, 699:2, 699:3, 699:4, 699:7, 699:8, 699:11, 699:16, 720:9, 720:20, 720:25, 721:13, 721:24, 726:3, 730:1, 730:11, 734:5, 734:8, 734:16, 748:19, 749:21, 754:19, 755:24, 757:17, 762:13, 780:12, 780:14, 780:16, 781:7, 781:9, 792:15, 792:19, 792:25, 793:2, 798:14, 798:25, 809:6, 829:8, 829:25, 832:22, 835:14, 835:17, 842:9, 845:7, 845:12, 853:1, 860:4, 862:22, 865:16, 872:11, 873:18, 876:14, 893:21, 900:17, 900:22, 903:19, 904:17, 917:16, 917:18, 917:23, 918:20, 919:4, 919:11, 919:17, 920:15, 920:18, 931:2, 931:5, 941:21, 947:2, 947:25, 948:24, 959:7</p> <p>articles [5] - 703:6, 703:9, 716:3, 865:10, 890:22</p> <p>articulated [4] - 734:15, 751:1, 771:15, 771:20</p> <p>articulation [1] - 911:18</p> <p>artisan [6] - 890:25,</p>	<p>891:6, 892:12, 892:13, 892:15, 893:9</p> <p>artist [1] - 676:2</p> <p>aside [1] - 816:5</p> <p>asleep [24] - 707:12, 802:9, 889:23, 890:8, 890:9, 890:19, 891:5, 891:8, 891:10, 891:16, 891:21, 891:24, 891:25, 892:1, 892:4, 892:6, 892:14, 892:21, 892:25, 893:1, 893:2, 893:3, 893:7</p> <p>aspect [10] - 675:9, 675:10, 675:24, 676:11, 682:11, 952:7, 955:4, 955:12, 955:15, 956:1</p> <p>aspects [1] - 936:17</p> <p>asserted [6] - 732:22, 761:2, 800:5, 935:20, 939:19, 939:20</p> <p>asserting [2] - 938:20, 939:17</p> <p>assertion [1] - 692:6</p> <p>assess [1] - 703:16</p> <p>assessed [2] - 925:23, 926:9</p> <p>assessing [2] - 789:7, 799:11</p> <p>assessment [1] - 842:4</p> <p>assist [2] - 701:4, 950:4</p> <p>associate [1] - 701:15</p> <p>associated [6] - 867:15, 878:9, 919:21, 946:19, 969:20, 969:21</p> <p>Association [2] - 702:4, 702:5</p> <p>association [3] - 951:18, 953:13, 953:21</p> <p>assume [4] - 802:8, 891:9, 905:9, 1002:23</p> <p>assumed [1] - 956:12</p> <p>assumes [1] - 992:22</p> <p>assuming [4] - 680:23, 680:24, 741:15, 943:14</p> <p>astronauts [1] - 898:7</p> <p>asymmetric [1] - 945:19</p>	<p>attached [7] - 762:17, 762:22, 762:25, 765:16, 767:4, 776:1, 797:22</p> <p>attaches [1] - 770:5</p> <p>attack [2] - 696:3, 696:4</p> <p>attempt [7] - 707:12, 731:23, 777:16, 784:24, 900:4, 901:13, 902:12</p> <p>attempted [1] - 769:9</p> <p>attempting [1] - 804:13</p> <p>attempts [1] - 899:7</p> <p>attend [1] - 1002:17</p> <p>attention [4] - 840:4, 840:7, 968:2, 989:21</p> <p>attest [1] - 755:20</p> <p>Attorney [1] - 701:13</p> <p>attorneys [2] - 800:25, 815:19</p> <p>attracted [2] - 840:4, 840:6</p> <p>attributable [1] - 856:7</p> <p>audience [1] - 835:17</p> <p>August [3] - 770:3, 780:23, 781:4</p> <p>authentic [1] - 748:9</p> <p>authenticate [2] - 734:4, 770:18</p> <p>authenticated [1] - 752:11</p> <p>authenticating [3] - 745:3, 795:10, 795:16</p> <p>authentication [3] - 743:7, 771:20, 772:1</p> <p>authenticity [8] - 736:18, 736:24, 750:15, 750:18, 751:10, 752:8, 770:24, 790:13</p> <p>author [19] - 703:11, 716:3, 718:13, 829:15, 839:14, 839:20, 852:16, 900:7, 903:25, 904:5, 904:9, 904:10, 904:12, 904:14, 906:5, 906:8, 906:11, 928:10</p> <p>authored [2] - 897:12, 925:17</p> <p>authors [9] - 699:7, 829:12, 842:13, 871:19, 903:19, 910:24, 919:4,</p>
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<p>946:13, 958:11 automatic [2] - 781:14, 797:18 automatically [5] - 778:23, 780:14, 781:10, 793:2, 797:22 availability [4] - 733:11, 751:22, 752:1, 761:21 available [25] - 674:12, 678:18, 694:20, 734:1, 735:23, 743:17, 751:15, 753:23, 754:5, 754:7, 754:12, 758:4, 766:16, 769:4, 773:13, 776:15, 785:11, 788:8, 789:14, 792:11, 795:2, 872:19, 873:19, 894:16 average [2] - 708:8, 789:3 avoid [2] - 806:7, 821:25 awake [8] - 707:12, 889:16, 890:8, 890:10, 890:18, 891:16, 892:25, 893:8 awaken [3] - 802:11, 802:23, 892:7 aware [8] - 672:8, 705:16, 710:16, 712:10, 955:18, 957:21, 985:23, 1002:19</p>	<p>962:23 based [22] - 685:10, 685:13, 726:7, 730:14, 730:21, 735:13, 738:21, 750:17, 794:14, 814:18, 815:18, 822:6, 883:5, 884:9, 887:4, 942:19, 946:6, 953:4, 974:12, 978:9, 979:25, 991:18 basis [10] - 691:4, 733:19, 782:13, 782:18, 794:22, 795:1, 796:5, 890:7, 946:15, 975:22 batch [2] - 680:6, 680:9 bearing [1] - 737:25 beat [2] - 706:7 beat-to-beat [1] - 706:7 became [7] - 692:5, 692:8, 692:23, 693:17, 795:2, 946:24, 949:10 become [8] - 692:9, 692:12, 695:14, 695:23, 697:19, 699:15, 915:13, 957:21 becomes [2] - 695:8, 908:17 bed [4] - 802:24, 848:18, 893:5 bedtime [28] - 727:22, 728:2, 773:3, 773:6, 773:10, 789:2, 797:9, 807:19, 808:3, 808:14, 813:1, 813:5, 816:24, 817:2, 818:13, 818:15, 821:11, 821:13, 821:14, 823:16, 824:1, 848:17, 867:16, 916:8, 916:9, 920:2, 923:15, 927:4 BEFORE [1] - 1:18 begin [3] - 803:11, 803:17, 822:8 beginning [10] - 672:4, 771:15, 830:14, 835:13, 851:21, 868:6, 868:9, 895:15, 910:13, 1002:5 begins [4] - 753:7,</p>	<p>867:25, 941:24, 999:19 behalf [2] - 700:21, 703:4 behavioral [1] - 706:5 behind [3] - 764:16, 764:19, 903:13 beings [4] - 838:4, 839:3, 840:12, 863:14 below [8] - 780:3, 780:6, 780:20, 893:17, 929:7, 993:5, 995:17, 997:13 bench [3] - 672:3, 696:23, 742:19 Bench [1] - 1:15 beneficial [2] - 672:11, 874:13 benefit [2] - 684:12, 692:1 Bergmeier [29] - 673:14, 674:7, 938:1, 942:17, 947:17, 949:22, 950:2, 951:13, 953:1, 959:18, 959:22, 961:22, 962:3, 963:5, 963:14, 964:9, 965:24, 966:2, 966:17, 966:19, 967:5, 967:24, 968:20, 968:25, 972:19, 973:11, 984:15, 984:17, 984:23 Bergmeier's [2] - 940:25, 941:19 best [4] - 691:11, 775:3, 845:10, 918:14 bet [1] - 749:8 better [6] - 696:6, 737:21, 824:22, 845:13, 889:25, 941:14 between [27] - 682:6, 706:19, 771:6, 789:10, 794:23, 801:5, 834:19, 857:7, 858:21, 862:7, 862:15, 871:21, 886:16, 892:25, 894:3, 897:5, 922:24, 936:6, 946:13, 970:18, 970:20, 971:14, 971:21,</p>	<p>971:22, 985:21, 989:15, 996:7 Beyond [1] - 789:19 big [8] - 675:3, 811:11, 839:25, 843:14, 843:16, 885:16, 887:21, 887:22 bigger [3] - 826:5, 887:23, 921:6 biggest [1] - 729:1 binary [5] - 889:21, 890:2, 890:11, 890:21, 891:4 bind [4] - 710:2, 722:4, 727:17, 857:21 binder [37] - 712:23, 713:25, 714:24, 716:6, 718:25, 720:4, 721:8, 723:14, 731:1, 774:8, 778:4, 779:11, 797:13, 826:11, 829:4, 849:18, 852:7, 880:7, 900:15, 902:7, 903:14, 906:3, 910:20, 917:12, 918:18, 920:7, 925:12, 947:8, 957:14, 965:8, 966:14, 973:15, 975:2, 980:11, 984:20, 994:4, 1002:11 binders [2] - 895:19, 924:19 binds [4] - 813:23, 858:1, 859:4, 859:7 biological [22] - 707:24, 708:3, 709:3, 709:5, 709:19, 709:23, 710:24, 712:14, 712:18, 728:21, 729:11, 810:12, 814:25, 836:4, 841:19, 868:6, 868:9, 869:5, 870:13, 896:11, 916:20 biology [1] - 896:10 biphasic [1] - 890:17 bit [35] - 701:11, 702:20, 703:25, 704:20, 705:23, 705:25, 712:7, 724:21, 756:5, 756:17, 779:23, 783:23, 791:6,</p>	<p>791:10, 791:14, 791:25, 801:15, 810:21, 813:20, 826:4, 831:7, 835:4, 840:16, 847:4, 858:12, 862:9, 868:6, 868:21, 869:19, 869:20, 869:22, 899:20, 976:24, 986:6, 997:23 black [1] - 984:20 BLAKE [1] - 671:16 blank [1] - 792:12 Blind [5] - 778:18, 789:19, 829:9, 850:17, 900:23 blind [63] - 707:22, 719:19, 719:22, 720:24, 722:25, 723:5, 731:11, 773:3, 773:6, 773:10, 797:12, 799:11, 803:20, 804:10, 806:18, 808:23, 809:5, 809:7, 809:10, 809:12, 811:7, 813:21, 817:7, 817:9, 818:17, 818:19, 821:6, 821:8, 830:16, 839:3, 846:20, 852:21, 854:20, 854:23, 897:1, 898:20, 899:8, 901:13, 902:12, 902:22, 904:19, 905:14, 906:15, 914:24, 919:19, 921:11, 921:25, 922:17, 925:23, 926:9, 926:23, 927:9, 927:20, 928:15, 928:17, 928:22, 929:12, 930:9, 930:13, 932:15, 934:2, 935:10, 937:7 blow [19] - 826:22, 883:25, 934:11, 958:10, 959:16, 959:21, 959:22, 961:19, 962:1, 963:3, 963:12, 964:5, 966:23, 967:3, 968:24, 969:4, 974:16, 976:1, 981:10 blue [8] - 816:14,</p>
B				
<p>bachelor's [2] - 896:10, 954:6 back-and-forth [3] - 770:22, 771:5, 775:14 background [4] - 701:21, 756:5, 826:22, 896:9 backward [2] - 837:3, 837:17 baffling [1] - 912:18 bar [9] - 870:23, 871:5, 871:21, 871:22, 871:25, 884:14 bars [2] - 707:6, 708:11 base [2] - 835:16,</p>				

<p>816:17, 818:10, 819:10, 821:5, 823:2, 871:21, 888:23 BMS [101] - 674:15, 674:22, 675:17, 675:22, 676:13, 678:3, 679:8, 680:6, 681:11, 681:16, 681:21, 682:4, 682:11, 682:13, 682:14, 682:16, 683:7, 685:22, 687:2, 687:4, 687:6, 687:11, 687:12, 687:22, 688:1, 688:2, 688:13, 689:7, 689:25, 690:5, 690:19, 690:22, 691:13, 692:5, 692:8, 692:12, 692:21, 692:25, 693:1, 693:2, 693:3, 693:6, 693:16, 694:8, 694:21, 694:24, 697:18, 699:3, 699:7, 699:8, 699:11, 725:23, 938:6, 939:21, 940:8, 940:15, 940:17, 940:19, 945:10, 946:3, 946:4, 946:6, 946:9, 946:14, 946:19, 946:21, 947:25, 948:10, 949:2, 950:16, 951:3, 951:25, 952:19, 956:7, 956:14, 957:4, 957:10, 958:13, 966:22, 968:4, 968:8, 968:11, 968:12, 969:6, 969:16, 969:19, 970:12, 970:17, 972:6, 988:5, 989:3, 989:6, 989:23, 990:9, 990:24, 995:25 BMS's [18] - 679:20, 680:5, 680:19, 681:4, 694:4, 698:7, 698:11, 698:16, 938:13, 940:10, 941:21, 951:1, 960:18, 967:14, 967:19, 967:20, 969:15, 971:5 board [3] - 753:11, 753:12, 823:18</p>	<p>Bob [4] - 715:21, 887:7, 891:17, 891:18 bobbing [1] - 892:4 body [27] - 706:14, 708:6, 708:23, 831:10, 831:15, 831:20, 831:24, 832:14, 836:13, 837:5, 837:6, 841:2, 842:6, 850:22, 850:23, 857:14, 857:21, 867:11, 868:8, 868:14, 868:23, 869:3, 869:4, 874:5, 874:8, 881:10, 912:5 body's [1] - 868:4 bond [5] - 970:18, 970:20, 970:24, 971:1, 971:2 book [7] - 854:8, 859:13, 864:20, 872:5, 876:4, 877:17, 880:15 borne [1] - 687:20 Boston [1] - 896:4 bottom [25] - 707:20, 708:9, 738:21, 746:5, 746:10, 746:11, 756:3, 778:6, 780:10, 786:14, 786:22, 808:16, 815:23, 845:23, 866:11, 873:5, 933:16, 934:11, 966:4, 967:11, 969:4, 970:25, 976:1, 986:4, 999:17 box [2] - 911:13, 912:1 brain [13] - 697:1, 706:8, 707:25, 867:21, 869:15, 890:6, 890:7, 890:9, 890:18, 891:18, 892:5, 924:9 break [5] - 776:22, 828:7, 895:5, 895:9, 1003:11 breaking [1] - 801:23 breath [1] - 890:14 Brief [4] - 791:4, 791:14, 791:16 brief [1] - 738:11 briefing [8] - 672:12, 672:25, 691:21, 701:9, 751:4, 751:8, 772:5, 772:12 briefly [14] - 701:20,</p>	<p>702:11, 706:2, 707:21, 723:14, 793:10, 800:12, 802:10, 815:10, 882:11, 886:18, 904:6, 924:1, 935:25 Brigham [4] - 702:15, 896:3, 897:20, 897:22 bring [13] - 674:22, 689:16, 694:8, 738:3, 738:8, 755:17, 758:18, 777:20, 783:2, 946:18, 994:3, 999:5 bringing [1] - 689:18 Bristol [1] - 674:10 Bristol-Myers [1] - 674:10 broader [1] - 758:12 broadly [3] - 722:1, 726:1, 869:3 broken [1] - 881:9 Brooks [1] - 925:13 brooks [19] - 783:6, 784:1, 784:8, 784:14, 786:18, 787:6, 792:8, 826:2, 826:20, 882:12, 883:24, 884:25, 986:3, 989:18, 990:20, 994:3, 997:19, 999:12, 1001:6 brought [4] - 682:1, 694:16, 694:23, 842:13 browser [1] - 783:7 BRYON [1] - 671:4 building [1] - 676:23 builds [1] - 676:2 built [1] - 676:16 bullet [5] - 882:16, 914:10, 954:20, 954:23, 955:14 bunch [1] - 779:19 burden [5] - 691:9, 692:1, 745:8, 748:16, 796:19 Burgess [1] - 837:13 business [1] - 760:23 but.. [1] - 680:15 BY [115] - 671:3, 671:8, 671:12, 671:15, 700:24, 711:21, 712:11, 713:13, 714:15, 715:15, 717:19, 718:23, 719:13, 720:19, 721:23,</p>	<p>724:3, 725:20, 727:4, 730:10, 778:3, 782:4, 782:22, 783:10, 783:19, 784:2, 784:9, 784:15, 786:10, 786:23, 787:8, 787:15, 790:16, 791:7, 791:15, 792:1, 792:9, 792:24, 793:13, 796:8, 796:23, 798:10, 798:23, 826:6, 826:24, 828:25, 830:11, 835:12, 835:22, 836:24, 838:13, 840:21, 845:6, 846:5, 847:16, 847:22, 850:14, 851:23, 852:15, 853:9, 855:11, 856:14, 860:3, 860:20, 861:9, 863:8, 863:21, 865:1, 866:13, 870:25, 872:7, 872:17, 873:6, 876:25, 880:14, 881:25, 882:19, 884:1, 884:16, 885:2, 895:24, 898:23, 901:10, 901:19, 902:19, 903:18, 904:7, 905:22, 906:7, 907:11, 908:3, 909:8, 911:9, 919:10, 924:23, 925:15, 934:17, 936:2, 950:1, 951:12, 952:25, 957:3, 958:8, 959:6, 961:14, 965:3, 965:23, 968:19, 972:18, 974:5, 975:16, 981:1, 981:21, 984:14, 999:13, 1001:25 byproduct [1] - 683:25</p>	<p>capable [7] - 838:23, 839:2, 862:19, 862:22, 862:25, 863:13, 982:20 capture [3] - 744:6, 744:11, 744:13 captured [3] - 762:12, 763:20, 763:23 captures [2] - 744:2, 762:2 carbons [5] - 970:18, 970:20, 971:13, 971:15, 971:21 carboxamide [11] - 675:12, 690:7, 945:22, 960:9, 960:13, 960:14, 962:10, 962:14, 962:16, 1001:15, 1001:20 Care [1] - 701:14 care [2] - 815:8, 818:20 cared [1] - 688:3 carries [1] - 1002:4 carry [1] - 977:19 carrying [1] - 746:6 cartoon [1] - 912:22 case [63] - 672:21, 673:6, 673:18, 673:23, 674:1, 674:3, 679:4, 679:12, 679:21, 686:11, 700:15, 702:21, 703:4, 703:15, 704:8, 706:15, 710:14, 711:10, 721:13, 730:1, 734:11, 737:25, 741:20, 743:15, 752:4, 752:6, 753:9, 758:1, 759:19, 772:19, 772:20, 774:1, 785:20, 790:23, 794:16, 796:18, 800:9, 830:12, 837:12, 843:1, 862:5, 862:16, 867:15, 886:5, 894:15, 894:18, 895:15, 897:5, 908:12, 910:2, 916:11, 938:2, 939:16, 957:25, 963:20, 965:2, 984:4, 987:19, 987:20, 988:2, 996:11, 1001:9, 1003:19</p>
C				
<p>calendar [1] - 893:16 candidate [2] - 961:24, 965:1 candidates [1] - 964:11 candidly [1] - 695:25 cannot [4] - 745:20, 749:2, 758:1, 924:14</p>				

<p>cases [2] - 735:15, 910:6</p> <p>cast [1] - 797:25</p> <p>categories [1] - 834:8</p> <p>category [1] - 864:5</p> <p>Catt [4] - 724:18, 724:23, 724:25, 974:13</p> <p>causality [1] - 868:19</p> <p>caused [6] - 729:10, 771:9, 883:12, 883:14, 883:15, 946:24</p> <p>causes [4] - 831:9, 831:10, 868:20, 883:13</p> <p>causing [2] - 719:24, 848:9</p> <p>centers [3] - 887:25, 888:2</p> <p>central [1] - 1001:23</p> <p>Central [1] - 746:24</p> <p>certain [7] - 705:3, 752:7, 764:13, 771:25, 831:9, 897:6, 946:15</p> <p>certainly [15] - 684:1, 710:9, 763:9, 805:2, 813:17, 828:20, 842:12, 845:16, 859:11, 862:14, 918:6, 918:13, 955:22, 997:6, 1002:23</p> <p>certify [1] - 1003:24</p> <p>chain [1] - 934:8</p> <p>challenge [2] - 683:5, 749:19</p> <p>challenging [2] - 749:20, 861:3</p> <p>chance [4] - 718:5, 852:14, 939:5, 943:8</p> <p>chances [1] - 718:3</p> <p>change [7] - 687:10, 764:15, 886:4, 956:3, 965:14, 966:4, 1003:10</p> <p>changed [3] - 786:16, 916:7, 967:14</p> <p>Changes [12] - 741:11, 747:3, 755:7, 785:11, 785:24, 786:14, 786:25, 787:3, 787:9, 787:19, 788:9, 789:14</p> <p>changes [9] - 740:7, 740:17, 744:17, 745:18, 756:8, 767:20, 768:10,</p>	<p>789:7, 985:22</p> <p>characterization [1] - 689:9</p> <p>characterized [2] - 688:10, 908:11</p> <p>Charles [2] - 702:14, 703:3</p> <p>Charmane [1] - 829:15</p> <p>chart [8] - 870:23, 884:14, 909:18, 920:14, 923:5, 968:14, 994:12</p> <p>check [1] - 709:3</p> <p>chemical [7] - 683:1, 831:11, 959:12, 970:18, 971:13, 990:7, 995:8</p> <p>chemically [1] - 972:2</p> <p>chemist [1] - 673:14</p> <p>chemistry [5] - 940:12, 954:6, 955:1, 966:21</p> <p>chemists [1] - 693:8</p> <p>Chief [1] - 1:18</p> <p>Chinese [9] - 973:9, 974:13, 980:1, 997:25, 998:6, 998:16, 1001:7, 1001:8</p> <p>chloride [3] - 962:22, 963:21, 963:23</p> <p>choice [3] - 721:3, 931:10, 996:6</p> <p>choices [2] - 708:22, 823:19</p> <p>chose [3] - 709:4, 885:24, 990:15</p> <p>chromatogram [2] - 688:10, 987:9</p> <p>chromatograms [1] - 688:8</p> <p>chromatographic [1] - 984:24</p> <p>chromatography [2] - 989:25, 990:3</p> <p>chromidiotic [1] - 727:18</p> <p>chronic [2] - 805:25, 879:25</p> <p>Chronobiotic [1] - 863:7</p> <p>chronology [3] - 687:20, 898:14, 900:11</p> <p>circadian [119] - 700:18, 702:9, 702:13, 702:23, 702:25, 703:7, 703:10, 704:25, 706:2, 706:3,</p>	<p>706:10, 706:13, 706:17, 706:18, 706:22, 707:7, 707:13, 707:15, 707:16, 708:17, 708:21, 709:6, 710:4, 712:1, 713:21, 713:23, 720:2, 720:23, 722:7, 722:10, 722:13, 722:18, 724:5, 725:1, 726:10, 727:24, 728:1, 729:5, 730:17, 730:18, 789:10, 799:17, 799:24, 803:25, 804:2, 804:11, 805:8, 805:10, 805:12, 810:17, 811:3, 812:5, 812:8, 814:13, 814:24, 815:1, 822:25, 830:22, 832:16, 836:4, 837:6, 839:3, 841:24, 842:4, 844:8, 844:9, 847:3, 847:12, 848:13, 850:20, 852:22, 854:22, 862:3, 862:4, 862:7, 862:15, 875:8, 883:2, 887:18, 888:13, 896:6, 896:21, 896:22, 897:1, 897:2, 897:7, 897:10, 898:20, 899:9, 899:22, 900:5, 914:23, 915:4, 915:18, 916:5, 916:17, 916:20, 916:23, 916:25, 920:19, 924:11, 925:23, 925:24, 926:10, 926:24, 927:9, 927:19, 928:15, 928:22, 930:9, 931:15, 932:4, 932:15, 933:5, 935:10, 937:7</p> <p>Circadian [1] - 918:21</p> <p>Circadin [3] - 873:23, 873:25, 874:15</p> <p>circle [1] - 898:10</p> <p>Circuit [4] - 749:3, 751:25, 754:5, 796:2</p> <p>Circuit's [1] - 751:23</p> <p>circulating [1] - 869:2</p> <p>circulation [3] -</p>	<p>913:16, 913:21, 914:3</p> <p>circumstances [7] - 692:22, 693:14, 693:15, 764:13, 788:4, 848:24, 897:6</p> <p>citation [5] - 754:22, 779:2, 780:12, 792:15, 792:18</p> <p>citations [1] - 754:18</p> <p>cite [2] - 796:3, 814:4</p> <p>cited [4] - 733:22, 750:20, 750:24, 957:22</p> <p>cites [8] - 739:11, 739:12, 929:17, 929:20, 929:25, 930:17, 932:18, 933:8</p> <p>citing [1] - 937:8</p> <p>CIVIL [1] - 1:5</p> <p>Claim [75] - 680:22, 681:5, 682:16, 724:22, 724:25, 725:3, 725:4, 800:10, 800:13, 800:14, 801:17, 803:10, 803:14, 804:9, 805:7, 807:13, 807:15, 808:21, 809:19, 810:1, 810:24, 813:12, 816:12, 817:10, 817:12, 817:18, 818:23, 819:3, 819:4, 819:6, 819:7, 819:16, 819:17, 819:18, 820:13, 820:15, 820:21, 820:22, 821:1, 821:10, 821:11, 821:13, 821:20, 821:21, 821:22, 822:3, 822:10, 822:15, 822:17, 822:20, 822:21, 822:22, 822:23, 823:3, 824:6, 824:19, 824:20, 825:13, 825:17, 942:12, 943:12, 952:11, 953:2, 954:1, 954:2, 956:9, 956:17, 957:7, 972:22, 980:4, 1000:11, 1001:12, 1002:5</p> <p>claim [24] - 680:23, 682:12, 684:25, 747:9, 748:13,</p>	<p>773:17, 800:3, 801:1, 801:9, 801:21, 815:19, 815:20, 815:21, 816:1, 817:23, 820:21, 823:12, 894:20, 948:11, 972:10, 1001:11, 1002:2, 1002:3, 1002:24</p> <p>claimed [8] - 773:8, 801:6, 810:1, 813:16, 950:23, 978:5, 978:21, 1001:12</p> <p>claiming [3] - 676:24, 824:16, 979:5</p> <p>claims [10] - 693:19, 728:4, 748:12, 800:6, 801:15, 801:18, 807:11, 816:4, 883:1, 935:20</p> <p>Claims [2] - 822:18, 974:10</p> <p>clarify [4] - 739:15, 772:18, 841:18, 856:21</p> <p>clarifying [1] - 699:17</p> <p>clarity [7] - 689:14, 691:20, 691:25, 816:18, 818:7, 920:4, 998:21</p> <p>clear [28] - 680:17, 688:5, 691:10, 691:17, 691:24, 692:2, 692:17, 703:2, 710:23, 721:2, 722:24, 723:1, 742:23, 747:14, 752:5, 757:21, 759:23, 772:3, 796:19, 805:25, 810:18, 854:18, 854:22, 857:2, 916:18, 920:25, 945:12, 999:14</p> <p>cleared [2] - 874:8, 913:23</p> <p>clearly [17] - 723:3, 734:23, 770:8, 785:24, 803:19, 804:10, 806:2, 806:19, 809:12, 811:10, 811:13, 812:17, 812:19, 814:2, 814:20, 817:1, 975:23</p> <p>click [17] - 740:20, 741:11, 747:2,</p>
---	--	--	---	--

<p>755:8, 767:24, 768:9, 783:16, 783:17, 783:25, 784:4, 784:7, 784:10, 784:13, 787:3, 787:5, 787:10, 787:14 clicking [1] - 786:14 climb [1] - 868:11 clinic [2] - 885:7, 888:5 clinical [46] - 736:9, 736:11, 739:14, 739:16, 740:5, 740:6, 746:21, 759:8, 761:15, 773:1, 778:10, 778:11, 780:15, 785:9, 788:23, 789:12, 789:23, 790:1, 790:9, 790:17, 790:21, 792:19, 794:15, 798:4, 799:14, 800:22, 815:12, 816:8, 816:20, 816:23, 816:25, 817:4, 817:6, 817:24, 818:8, 879:12, 879:20, 880:16, 885:23, 885:24, 887:16, 917:4, 920:3, 925:9, 964:11, 964:25 Clinical [2] - 918:20, 961:17 clinicaltrials.gov [42] - 731:7, 731:8, 740:1, 740:6, 740:15, 741:4, 742:7, 743:19, 745:10, 747:11, 748:14, 749:10, 755:3, 755:12, 758:13, 761:18, 763:12, 767:6, 767:15, 767:20, 768:16, 770:4, 770:6, 775:5, 778:12, 778:24, 782:23, 783:2, 784:3, 784:25, 785:6, 785:12, 785:25, 787:2, 788:10, 789:15, 789:17, 793:3, 816:10, 816:15, 817:8, 818:4 clinicaltrials.gov's [1] - 765:16</p>	<p>clinicaltrials.org [2] - 785:10, 789:13 clinicians [1] - 708:16 clinics [2] - 888:6 clock [61] - 707:24, 707:25, 708:5, 709:5, 709:8, 709:11, 709:15, 709:19, 710:25, 712:18, 713:17, 715:23, 727:19, 728:21, 729:11, 730:17, 810:13, 814:24, 814:25, 830:22, 832:16, 836:4, 836:10, 836:12, 836:13, 836:16, 837:5, 837:6, 837:17, 841:19, 841:24, 844:1, 844:11, 844:12, 847:6, 867:18, 870:13, 899:19, 899:21, 902:25, 905:12, 905:18, 913:3, 913:7, 914:16, 914:21, 914:22, 915:5, 915:20, 916:4, 916:20, 918:11, 920:19, 922:15, 924:11, 932:4, 933:5 close [4] - 758:25, 839:7, 987:13, 987:15 closer [1] - 841:14 closing [1] - 1003:7 closings [1] - 672:9 CN019 [1] - 997:25 CN268 [10] - 953:3, 953:6, 953:16, 978:13, 978:14, 978:18, 979:6, 979:16, 979:18, 1002:3 co-elution [2] - 987:11, 987:19 co-elute [2] - 968:10, 992:8 coauthored [1] - 897:11 COBLENTZ [14] - 671:16, 898:21, 901:6, 902:14, 911:5, 919:7, 924:19, 924:23, 925:13, 925:15, 934:10, 934:17, 935:23, 984:2</p>	<p>cocktail [1] - 887:12 cocounsel [1] - 741:19 coding [3] - 801:20, 801:22, 821:1 cognizant [1] - 737:21 coin [1] - 842:7 coincident [1] - 913:18 coined [1] - 842:9 coinventor [1] - 685:23 coinventors [1] - 693:4 coinventorship [1] - 693:16 colleague [3] - 697:11, 758:18, 860:8 colleagues [11] - 714:6, 715:5, 725:11, 728:14, 850:1, 851:15, 851:24, 856:23, 902:11, 907:6, 912:3 collected [1] - 868:3 collecting [1] - 872:19 collectively [4] - 809:18, 813:11, 824:5, 851:8 College [1] - 701:22 COLM [1] - 1:18 color [4] - 801:20, 801:22, 801:24, 821:1 color-coding [3] - 801:20, 801:22, 821:1 column [13] - 753:8, 845:23, 846:2, 860:19, 925:20, 926:3, 930:6, 968:6, 985:20, 986:25, 987:4, 987:23, 994:25 columns [1] - 985:19 coma [3] - 889:4, 889:5, 889:13 combination [20] - 673:17, 800:15, 803:13, 805:21, 806:14, 807:21, 808:22, 809:18, 811:18, 813:10, 818:24, 819:1, 820:2, 820:16, 822:11, 822:13, 872:9, 938:21, 978:13, 979:11 combinations [12] -</p>	<p>712:9, 772:22, 803:9, 819:13, 819:24, 821:17, 822:4, 822:14, 824:3, 854:16, 876:8, 877:23 combine [6] - 801:13, 809:25, 810:18, 813:15, 814:3, 879:4 combined [4] - 810:20, 810:22, 814:8, 979:19 combining [1] - 879:7 combs [1] - 817:14 comfort [1] - 894:10 comfortable [1] - 941:9 coming [5] - 672:22, 675:1, 688:25, 768:17, 953:25 comments [1] - 937:4 commercial [1] - 683:23 commercial-grade [1] - 683:23 Commercialization [1] - 961:17 committee [2] - 829:20, 829:23 common [8] - 803:2, 819:6, 819:11, 820:22, 821:15, 855:1, 862:12, 897:4 commonalities [1] - 820:25 commonly [2] - 803:4, 839:5 commonsense [2] - 802:25, 803:5 companies [1] - 740:4 company [2] - 693:6, 740:14 compare [9] - 744:13, 768:9, 787:17, 790:25, 791:16, 791:21, 792:2, 833:24, 960:17 Compared [2] - 778:18, 789:19 compared [2] - 795:20, 804:24 comparing [3] - 788:13, 834:24, 970:2 comparison [4] - 834:6, 985:11, 985:25, 986:7 compilation [2] - 756:13, 778:10 compiled [1] - 756:8</p>	<p>complete [5] - 797:17, 798:7, 981:3, 981:6, 982:17 completed [2] - 672:12, 937:20 completes [1] - 882:9 complex [1] - 954:16 complicated [1] - 862:9 components [2] - 986:25, 987:4 composition [1] - 972:23 Compound [9] - 960:7, 962:12, 962:13, 962:16, 962:17, 962:21, 962:23, 962:24, 963:16 compound [11] - 673:4, 690:2, 959:20, 960:4, 960:5, 960:8, 962:14, 968:10, 971:11, 977:14, 989:13 compounds [11] - 951:18, 953:14, 953:21, 955:23, 966:13, 971:12, 976:7, 978:7, 978:9, 982:7, 983:16 comprises [1] - 972:23 compromise [1] - 849:1 computer [1] - 1003:20 concede [1] - 743:16 conceded [2] - 734:18, 940:18 conceive [1] - 951:2 conceived [1] - 950:23 concentration [1] - 847:24 Concept [1] - 838:15 concept [4] - 803:23, 815:25, 835:1, 850:19 conception [2] - 693:2, 951:3 concern [2] - 751:21, 757:18 concerned [1] - 753:18 concerning [1] - 733:10 concerns [4] - 883:7, 951:18, 953:13, 953:20</p>
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<p>conclude [14] - 685:6, 686:7, 713:18, 713:20, 719:21, 720:25, 722:15, 726:6, 730:20, 817:23, 820:6, 825:13, 846:19, 964:18</p> <p>concluded [4] - 726:7, 920:18, 952:24, 1003:22</p> <p>concludes [2] - 730:16, 814:22</p> <p>concluding [3] - 766:24, 819:22, 822:2</p> <p>conclusion [4] - 718:14, 800:1, 964:17, 964:20</p> <p>Conclusion [1] - 927:7</p> <p>conclusions [3] - 730:14, 820:14, 920:15</p> <p>conclusively [1] - 718:16</p> <p>condition [4] - 783:11, 783:15, 797:11, 851:12</p> <p>conditional [1] - 772:23</p> <p>conditionally [6] - 958:6, 958:19, 958:23, 964:23, 972:16</p> <p>conditions [5] - 984:24, 991:22, 992:1, 992:10, 992:16</p> <p>conducted [2] - 736:9, 739:17</p> <p>confer [4] - 685:15, 737:8, 764:9, 765:6</p> <p>conference [2] - 775:18, 887:11</p> <p>confess [1] - 912:18</p> <p>confidence [2] - 767:14, 894:11</p> <p>confident [1] - 752:5</p> <p>confidential [4] - 680:8, 692:21, 692:25, 693:14</p> <p>confirm [5] - 734:4, 796:24, 815:12, 878:12, 903:14</p> <p>confirms [1] - 930:12</p> <p>conflicted [1] - 924:1</p> <p>conflicting [2] - 710:17, 917:9</p> <p>conform [1] - 722:3</p>	<p>confronted [2] - 680:14, 785:21</p> <p>confused [6] - 674:22, 732:7, 762:19, 779:16, 931:25, 949:10</p> <p>confusing [2] - 710:17, 924:9</p> <p>confusion [2] - 946:24, 949:16</p> <p>connected [1] - 998:24</p> <p>connection [4] - 679:4, 680:2, 862:14, 862:15</p> <p>connectivity [2] - 971:14, 971:20</p> <p>CONNOLLY [1] - 1:18</p> <p>consciousness [1] - 889:18</p> <p>consensus [1] - 917:19</p> <p>consequences [1] - 774:16</p> <p>consequently [1] - 953:14</p> <p>consider [22] - 716:4, 737:3, 750:6, 750:8, 750:17, 751:9, 801:1, 801:2, 801:11, 801:12, 801:18, 819:4, 887:17, 909:10, 919:20, 954:3, 957:24, 972:25, 973:6, 973:22, 975:8, 980:7</p> <p>considerable [1] - 955:3</p> <p>considerations [5] - 711:11, 801:7, 955:19, 963:8, 980:4</p> <p>considered [6] - 750:16, 876:15, 877:12, 884:6, 926:18, 980:3</p> <p>considering [1] - 738:14</p> <p>consistent [2] - 798:1, 946:22</p> <p>constantly [1] - 744:6</p> <p>constructed [1] - 833:25</p> <p>constructing [1] - 835:6</p> <p>construction [5] - 800:3, 823:12, 894:21, 948:11, 1002:24</p> <p>construe [1] - 772:2</p>	<p>construes [1] - 693:18</p> <p>contact [2] - 943:12, 972:10</p> <p>contacting [12] - 680:25, 942:18, 943:14, 944:7, 947:14, 947:17, 947:21, 952:11, 952:14, 956:9, 956:16, 957:6</p> <p>Contacts [1] - 746:25</p> <p>Contacts/Locations [1] - 746:24</p> <p>contain [6] - 712:6, 739:17, 803:22, 827:8, 953:18, 978:22</p> <p>contained [2] - 761:17, 956:9</p> <p>contains [1] - 865:9</p> <p>contend [1] - 938:23</p> <p>contending [1] - 947:14</p> <p>content [6] - 731:21, 745:18, 747:16, 751:6, 789:23, 801:3</p> <p>contentions [2] - 759:11, 939:10</p> <p>contents [7] - 756:9, 758:1, 766:14, 766:25, 795:14, 795:15, 987:9</p> <p>contested [1] - 753:19</p> <p>context [9] - 697:18, 698:3, 698:7, 758:21, 939:16, 945:1, 949:7, 961:7, 995:7</p> <p>contingent [1] - 947:20</p> <p>continue [6] - 702:24, 806:8, 913:22, 921:3, 922:5, 951:13</p> <p>continues [1] - 943:17</p> <p>contract [4] - 677:10, 677:11, 687:13, 688:5</p> <p>contractually [1] - 687:7</p> <p>contradicting [1] - 696:24</p> <p>contradiction [1] - 944:15</p> <p>contradictory [1] - 939:7</p> <p>contrast [3] - 836:15, 859:7, 929:10</p> <p>contrasts [1] - 877:14</p> <p>contribute [2] - 677:3, 684:6</p>	<p>contributed [2] - 677:8, 687:19</p> <p>contribution [2] - 688:11, 693:1</p> <p>control [6] - 683:12, 708:5, 966:21, 983:9, 983:16, 983:23</p> <p>controlling [3] - 683:20, 919:21, 982:7</p> <p>controversially [1] - 932:3</p> <p>convenient [1] - 864:19</p> <p>conventionally [1] - 858:3</p> <p>conversation [2] - 884:17, 891:7</p> <p>conversations [1] - 1003:17</p> <p>convincing [3] - 691:10, 691:18, 692:2</p> <p>copies [1] - 762:23</p> <p>copy [7] - 753:2, 758:9, 758:18, 776:10, 777:6, 786:3, 829:5</p> <p>copying [1] - 934:19</p> <p>core [2] - 706:14, 708:6</p> <p>corner [6] - 738:22, 738:25, 747:18, 778:6, 835:21, 990:23</p> <p>correct [265] - 674:24, 681:3, 681:13, 688:12, 690:4, 695:1, 703:4, 707:19, 711:18, 725:3, 728:5, 732:12, 733:16, 734:5, 736:10, 748:5, 750:19, 763:15, 763:23, 763:24, 773:13, 774:15, 775:25, 776:10, 786:20, 794:5, 794:6, 794:7, 795:23, 796:1, 805:4, 805:16, 807:12, 808:9, 808:20, 812:12, 815:7, 829:10, 829:13, 829:17, 829:21, 830:25, 831:15, 831:20, 831:24, 832:3, 832:6, 832:24,</p>	<p>834:12, 834:20, 834:23, 835:5, 835:24, 836:6, 836:10, 836:11, 836:17, 836:25, 837:3, 837:8, 837:21, 837:22, 837:25, 838:16, 838:20, 838:21, 838:24, 838:25, 839:3, 839:4, 839:9, 839:15, 839:20, 839:21, 839:23, 839:24, 840:24, 840:25, 841:4, 841:5, 841:8, 841:12, 841:17, 841:21, 841:25, 842:3, 842:23, 843:3, 843:12, 843:18, 843:23, 844:4, 844:8, 844:14, 844:19, 845:14, 846:10, 846:13, 846:17, 847:12, 848:1, 848:10, 848:18, 851:5, 851:13, 852:12, 852:17, 853:4, 853:11, 853:18, 854:19, 854:25, 855:3, 855:18, 855:21, 855:22, 855:25, 856:1, 856:4, 856:24, 857:10, 857:24, 858:1, 858:5, 858:16, 858:19, 858:23, 858:24, 859:2, 859:5, 859:6, 859:9, 859:11, 859:24, 859:25, 860:5, 860:6, 860:9, 861:14, 861:15, 861:17, 861:19, 862:3, 862:21, 863:15, 864:6, 864:18, 865:4, 865:5, 865:7, 865:8, 865:10, 866:16, 866:17, 866:19, 866:21, 866:22, 866:24, 866:25, 867:2, 867:3, 867:4, 867:12, 868:25, 869:17, 870:2, 870:9, 870:10, 870:18, 871:13, 871:17, 871:22, 873:8, 873:15,</p>
---	---	--	---	---

873:16, 873:20,
873:21, 874:19,
874:22, 875:14,
875:15, 876:8,
877:2, 877:4, 877:7,
877:9, 877:10,
877:15, 877:16,
877:23, 878:4,
878:7, 878:10,
880:1, 880:2, 882:8,
882:24, 886:21,
896:18, 902:2,
903:20, 904:2,
904:15, 906:9,
909:11, 911:25,
912:11, 916:5,
919:2, 920:13,
920:19, 920:20,
921:20, 925:1,
925:4, 925:5, 925:7,
925:8, 925:10,
925:11, 925:17,
926:5, 926:12,
926:16, 926:19,
927:5, 927:11,
927:25, 928:3,
928:8, 928:10,
928:16, 928:24,
929:4, 929:18,
929:25, 930:3,
930:17, 930:20,
930:21, 930:23,
931:2, 931:15,
932:18, 932:21,
932:24, 933:13,
935:1, 935:21,
935:22, 936:21,
942:6, 964:21,
970:13, 971:24,
972:2, 988:3,
993:17, 994:10,
996:10, 996:17,
996:23, 997:11,
998:11, 1002:7
correctable [3] -
686:1, 686:8, 686:21
corrected [1] - 688:15
correcting [1] - 720:1
correction [1] - 739:20
correctly [2] - 928:23,
985:14
correlation [3] -
833:18, 833:21,
862:7
correspond [2] -
816:12, 963:23
corresponds [2] -
827:5, 969:14
corroborates [3] -
766:13, 766:16,

768:7
cortisol [4] - 706:13,
901:18, 901:20,
908:13
cost [2] - 963:9, 997:6
counsel [10] - 677:6,
685:17, 736:22,
737:11, 756:21,
772:7, 794:23,
828:13, 888:22,
951:22
counteract [4] -
709:12, 843:7,
843:8, 921:18
counteracted [1] -
914:8
country [3] - 888:1,
888:7, 888:8
couple [7] - 711:24,
724:22, 737:2,
764:22, 772:14,
910:17, 978:15
course [8] - 688:7,
688:19, 693:18,
693:24, 704:4,
796:15, 846:22,
922:20
court [7] - 704:7,
737:15, 785:3,
790:7, 896:16,
950:12, 998:12
COURT [417] - 1:2,
672:5, 672:13,
672:24, 673:5,
673:10, 673:21,
674:4, 674:21,
674:25, 675:6,
675:10, 675:15,
675:19, 676:7,
676:9, 676:17,
676:20, 676:22,
677:2, 677:6,
677:14, 677:18,
677:22, 678:8,
678:13, 678:23,
679:5, 680:16,
680:19, 680:22,
681:4, 681:7,
681:14, 681:20,
682:14, 682:16,
682:19, 682:22,
684:4, 684:14,
684:19, 685:6,
685:12, 685:16,
686:19, 687:1,
687:15, 689:3,
689:13, 689:18,
689:21, 689:23,
690:2, 690:11,
690:17, 691:7,

692:7, 692:19,
693:21, 694:1,
694:8, 694:12,
694:15, 694:23,
695:2, 695:4,
695:10, 695:17,
696:1, 696:6, 696:8,
696:10, 696:13,
696:17, 696:22,
697:3, 697:15,
697:21, 697:24,
698:5, 698:12,
698:20, 698:24,
699:19, 699:23,
700:3, 700:7, 700:9,
711:7, 711:12,
711:19, 713:11,
714:13, 715:13,
717:14, 718:18,
718:20, 719:11,
720:17, 721:21,
724:1, 725:18,
727:2, 730:8,
731:16, 732:5,
732:7, 732:18,
732:21, 733:5,
733:12, 733:17,
733:21, 734:2,
734:9, 734:14,
734:20, 735:3,
735:10, 735:20,
735:25, 736:3,
736:8, 736:11,
736:14, 736:20,
737:14, 738:16,
739:11, 739:19,
740:3, 740:8,
740:12, 741:2,
741:6, 741:9,
741:13, 741:22,
742:1, 742:9, 743:5,
743:21, 743:24,
744:4, 744:15,
744:20, 744:22,
744:25, 745:5,
745:13, 745:21,
746:8, 746:12,
747:9, 747:15,
747:20, 747:24,
748:3, 748:6, 749:4,
750:3, 750:20,
751:17, 752:3,
752:15, 752:20,
752:24, 753:3,
753:6, 753:17,
754:2, 754:8,
754:14, 754:23,
755:4, 755:10,
756:19, 756:23,
757:10, 758:5,
758:14, 758:17,

758:23, 759:4,
759:13, 760:4,
760:13, 761:9,
761:23, 762:5,
762:10, 762:15,
763:7, 763:10,
763:18, 763:21,
764:1, 764:4,
764:18, 765:9,
765:14, 765:20,
765:23, 766:10,
766:18, 766:21,
767:2, 768:2, 768:5,
768:12, 768:20,
769:6, 769:13,
769:16, 769:19,
769:22, 770:10,
770:13, 770:15,
772:9, 773:16,
773:21, 774:3,
774:6, 774:9,
774:12, 774:19,
774:24, 775:1,
775:12, 775:24,
776:6, 776:13,
776:17, 776:21,
776:24, 777:4,
777:8, 777:11,
777:13, 777:17,
777:20, 777:23,
778:2, 781:16,
781:23, 782:2,
782:15, 783:3,
783:5, 784:20,
785:4, 786:1, 786:5,
787:25, 788:5,
788:15, 788:18,
788:21, 792:23,
793:11, 795:5,
795:8, 795:18,
795:24, 796:4,
796:11, 797:15,
798:21, 828:6,
828:10, 828:21,
830:7, 844:25,
850:7, 880:9,
880:13, 881:19,
881:24, 882:10,
886:9, 886:14,
886:19, 886:22,
886:25, 887:4,
887:10, 887:20,
887:25, 888:9,
888:15, 888:17,
888:20, 888:25,
889:7, 889:15,
889:21, 890:22,
890:25, 891:4,
891:21, 892:8,
892:12, 892:14,
892:20, 892:24,

893:9, 893:12,
893:15, 894:5,
894:19, 894:23,
895:1, 895:8,
895:13, 895:17,
895:20, 898:22,
901:7, 902:15,
911:6, 919:8,
924:18, 924:21,
934:16, 935:24,
937:23, 938:4,
938:10, 938:18,
939:2, 939:8,
939:13, 940:1,
940:5, 940:13,
940:16, 940:21,
941:3, 941:6, 941:9,
941:14, 941:23,
941:25, 942:4,
942:7, 942:13,
942:16, 942:21,
943:4, 943:24,
944:4, 944:8,
944:18, 945:3,
945:5, 945:11,
945:15, 946:11,
946:17, 947:1,
947:10, 947:12,
947:19, 948:7,
948:13, 948:18,
948:21, 949:4,
949:11, 949:13,
949:19, 949:23,
951:8, 951:10,
951:21, 951:25,
952:8, 952:20,
956:21, 956:25,
958:5, 958:16,
959:3, 960:23,
961:1, 961:4, 961:9,
961:13, 964:15,
964:20, 964:22,
965:21, 972:16,
974:3, 975:14,
980:24, 981:17,
981:20, 984:4,
984:6, 984:9,
984:12, 998:5,
998:12, 998:16,
998:18, 998:25,
999:5, 999:9,
1001:22, 1002:13,
1002:22, 1003:2,
1003:6, 1003:15
Court [39] - 673:7,
681:19, 701:1,
707:5, 711:22,
712:10, 733:8,
737:22, 751:23,
753:15, 755:2,
758:22, 759:2,

761:5, 800:18,
800:20, 810:3,
817:22, 823:11,
825:13, 839:17,
894:10, 895:9,
896:1, 896:8, 899:6,
899:15, 902:1,
908:7, 912:13,
914:9, 923:5,
923:25, 944:14,
949:6, 949:7,
998:21, 1004:2
Court's [3] - 760:22,
783:1, 823:12
Courtroom [1] - 672:4
courtroom [12] -
736:17, 736:19,
736:21, 736:22,
736:23, 736:25,
760:24, 817:13,
825:5, 892:2, 950:9,
956:7
cover [16] - 701:7,
704:23, 704:24,
724:23, 724:25,
762:18, 762:25,
763:3, 763:13,
778:15, 865:2,
865:13, 865:17,
899:17, 905:20,
910:18
covered [4] - 685:15,
685:17, 905:20,
910:19
COVID [2] - 889:22
COZEN [1] - 671:15
crawled [1] - 744:10
crawls [1] - 744:1
create [4] - 686:17,
948:5, 958:23,
958:24
created [4] - 676:4,
692:15, 921:1, 921:2
credentials [2] -
701:8, 701:11
credibility [2] - 696:3,
696:5
credit [2] - 687:2,
842:10
credited [2] - 681:24,
693:1
criteria [1] - 780:4
critical [2] - 751:16,
753:24
critically [1] - 712:8
cross [23] - 679:16,
689:15, 691:12,
694:16, 694:17,
694:19, 694:24,
695:23, 696:16,

790:14, 793:10,
797:23, 828:13,
886:4, 895:7,
910:24, 914:20,
924:18, 924:19,
947:3, 947:8,
949:12, 984:10
CROSS [4] - 793:12,
828:24, 924:22,
984:13
cross-examination [9]
- 679:16, 689:15,
691:12, 790:14,
797:23, 886:4,
910:24, 914:20,
949:12
**CROSS-
EXAMINATION** [4] -
793:12, 828:24,
924:22, 984:13
cross-examine [1] -
793:10
crossover [3] -
827:25, 841:15,
926:23
CRR [2] - 1:24, 1004:2
crystal [1] - 999:20
cued [1] - 869:16
cull [6] - 804:4,
804:18, 812:21,
813:7, 879:16,
911:11
culled [9] - 805:3,
805:15, 807:10,
808:18, 812:10,
815:5, 823:24,
873:3, 873:7
culls [2] - 812:7, 815:2
culprit [1] - 853:11
current [5] - 701:12,
788:9, 789:15,
835:16, 931:10
Current [1] - 875:1
curve [17] - 833:23,
835:1, 835:24,
837:9, 837:24,
841:16, 843:3,
843:16, 843:17,
905:6, 905:15,
912:7, 912:10,
912:23, 912:24,
913:2, 916:24
curves [4] - 835:7,
835:8, 837:14,
905:10
cut [2] - 847:24, 895:6
CV [2] - 886:10,
886:11
cycle [7] - 804:16,
805:9, 805:19,

847:1, 847:5,
905:17, 912:21
Cycle [1] - 900:23
cycles [1] - 804:13
cyclopropanation [1]
- 945:20
CYP [1] - 705:3
CYP1A2 [4] - 819:21,
820:5, 881:4, 882:7
CYP3A4 [1] - 821:25
CYP3A4-related [1] -
820:10
cytochrome [1] -
704:17
Czeisler [6] - 702:14,
703:3, 705:16,
711:2, 711:23,
886:14
Czeisler's [2] -
705:21, 710:13

D

D) [1] - 961:18
daily [16] - 788:25,
802:3, 804:22,
821:10, 821:13,
823:2, 849:2,
855:24, 880:20,
925:22, 927:3,
929:13, 931:5,
931:9, 933:25,
994:13
DANIEL [1] - 671:10
dark [2] - 869:8,
869:15
darkness [2] - 868:25,
869:3
data [15] - 790:9,
825:23, 846:15,
884:9, 908:4, 908:9,
912:18, 912:20,
921:10, 922:7,
969:7, 986:8,
986:11, 988:20,
989:23
date [66] - 673:8,
674:13, 674:16,
674:19, 675:23,
676:13, 687:18,
691:14, 691:16,
694:25, 699:11,
731:24, 732:8,
732:14, 732:16,
733:24, 734:5,
735:18, 737:18,
739:2, 740:21,
741:1, 742:24,
743:1, 744:9,
744:14, 745:14,

746:16, 747:12,
749:13, 751:16,
752:7, 752:10,
753:24, 754:6,
754:12, 757:7,
759:2, 759:25,
762:3, 764:2, 764:6,
764:7, 764:17,
765:1, 766:17,
768:2, 771:25,
779:21, 780:1,
780:20, 780:22,
781:3, 787:12,
790:18, 790:20,
791:8, 794:1,
795:12, 850:13,
872:20, 910:13,
916:11, 917:10,
919:2
dated [4] - 738:23,
748:19, 749:21,
755:24
dates [6] - 739:4,
739:5, 745:20,
762:25, 763:4, 794:9
day-to-day [2] -
869:12, 904:10
days [2] - 690:25,
724:22
daytime [4] - 830:23,
832:18, 867:21,
931:16
DDI [1] - 881:3
DDX-419 [1] - 771:10
DDX-5.55 [1] - 800:8
DDX-5.9 [1] - 705:13
de [1] - 693:3
Deacon [4] - 713:3,
713:14, 713:18,
920:10
dead [1] - 890:16
deadline [2] - 758:25,
936:25
deal [4] - 672:22,
839:25, 976:22,
977:6
dealt [1] - 912:16
debate [12] - 676:19,
678:21, 723:7,
723:10, 723:12,
739:13, 755:15,
758:16, 858:9,
949:21, 1003:7
Deborah [2] - 903:23,
917:14
decade [1] - 838:7
December [5] - 673:4,
673:8, 673:9, 749:10
decide [7] - 672:15,
672:25, 693:20,

738:14, 790:13,
879:5, 958:24
decided [6] - 760:18,
865:15, 918:6,
918:13, 947:6, 947:7
deciding [1] - 948:9
decision [5] - 751:23,
753:11, 797:18,
797:24, 977:3
declarant [3] - 760:19,
767:11, 776:3
declaration [29] -
734:22, 735:2,
743:18, 743:21,
758:12, 759:4,
759:6, 759:17,
759:23, 760:2,
760:7, 760:15,
762:2, 762:6, 762:8,
762:16, 762:22,
766:8, 766:13,
766:15, 766:20,
766:22, 767:13,
768:7, 769:18,
769:20, 775:23,
776:8
decline [1] - 868:18
decreased [4] - 889:2,
889:5, 889:11,
889:13
Defendant [2] - 1:9,
700:21
defendant's [4] -
674:9, 761:12,
761:17, 950:13
defendants [6] -
673:17, 700:12,
732:3, 759:1,
761:14, 954:1
defined [2] - 893:1,
954:5
definitely [14] -
775:16, 810:2,
810:25, 818:1,
829:23, 835:7,
837:25, 840:2,
840:5, 841:9, 886:6,
887:8, 893:11,
932:10
definition [16] -
705:17, 705:21,
888:25, 889:7,
889:15, 954:14,
954:16, 954:18,
954:21, 955:5,
955:8, 955:12,
955:15, 956:1, 956:4
degree [6] - 701:22,
896:10, 925:1,
954:6, 954:17, 955:2

<p>DEIRDE ^[1] - 671:4</p> <p>Delaney ^[1] - 958:12</p> <p>DELAWARE ^[1] - 1:3</p> <p>Delaware ^[1] - 1:14</p> <p>delay ^[15] - 709:9, 836:16, 841:3, 841:15, 841:16, 843:3, 843:17, 851:4, 851:8, 905:8, 905:10, 908:12, 913:7, 914:6, 932:3</p> <p>delayed ^[1] - 844:12</p> <p>delays ^[1] - 843:6</p> <p>deleterious ^[1] - 883:7</p> <p>demonstrate ^[2] - 728:20, 897:9</p> <p>demonstrated ^[4] - 714:20, 753:18, 862:19, 883:21</p> <p>demonstrating ^[1] - 838:7</p> <p>demonstration ^[2] - 712:17, 926:8</p> <p>Demonstration ^[1] - 838:14</p> <p>demonstrative ^[6] - 707:2, 912:12, 950:4, 970:2, 973:3, 976:10</p> <p>demonstratively ^[1] - 697:6</p> <p>demonstratives ^[1] - 701:3</p> <p>density ^[1] - 890:6</p> <p>Department ^[1] - 701:17</p> <p>dependent ^[1] - 857:2</p> <p>depose ^[1] - 776:3</p> <p>deposition ^[14] - 677:19, 686:17, 690:21, 695:16, 695:24, 699:3, 699:6, 829:6, 833:17, 928:18, 940:18, 946:22, 947:18, 949:1</p> <p>depression ^[2] - 862:5, 862:8</p> <p>depth ^[1] - 907:25</p> <p>Deputy ^[1] - 701:13</p> <p>DEREK ^[1] - 671:17</p> <p>describe ^[3] - 706:2, 717:20, 728:18</p> <p>described ^[20] - 685:2, 757:12, 766:4, 799:13, 802:22, 813:19, 821:17, 898:13, 917:18, 954:23, 959:18, 961:22, 962:3,</p>	<p>963:5, 964:9, 965:2, 969:7, 974:20, 1000:14, 1002:4</p> <p>describes ^[4] - 728:19, 739:13, 813:4, 916:24</p> <p>describing ^[7] - 731:9, 731:10, 767:19, 901:11, 963:7, 1000:21, 1000:23</p> <p>description ^[5] - 809:3, 817:4, 824:9, 824:12, 825:21</p> <p>Description ^[1] - 791:20</p> <p>designated ^[1] - 738:19</p> <p>designed ^[1] - 964:25</p> <p>designing ^[1] - 963:8</p> <p>desire ^[2] - 706:20, 884:22</p> <p>desired ^[3] - 707:17, 810:7, 844:3</p> <p>despite ^[1] - 938:22</p> <p>detail ^[2] - 801:16, 824:14</p> <p>detailed ^[1] - 817:3</p> <p>Detailed ^[1] - 791:20</p> <p>details ^[2] - 696:21, 703:24</p> <p>detect ^[9] - 982:6, 986:13, 986:15, 986:17, 986:20, 987:7, 991:15, 992:23, 994:21</p> <p>detecting ^[1] - 992:17</p> <p>detection ^[1] - 985:6</p> <p>determination ^[2] - 948:9, 971:25</p> <p>determine ^[9] - 890:7, 905:1, 905:14, 950:25, 973:11, 982:25, 983:18, 991:17, 995:7</p> <p>determined ^[1] - 970:14</p> <p>determining ^[2] - 933:21, 955:10</p> <p>detract ^[1] - 692:23</p> <p>develop ^[1] - 693:7</p> <p>developed ^[2] - 830:2, 964:12</p> <p>Development ^[2] - 959:14, 961:16</p> <p>development ^[4] - 711:25, 861:1, 873:20, 959:24</p> <p>deviation ^[1] - 805:1</p> <p>diagnosed ^[1] - 925:3</p> <p>diagnosis ^[2] -</p>	<p>700:16, 829:8</p> <p>diaries ^[1] - 891:15</p> <p>difference ^[6] - 682:4, 871:21, 894:3, 911:21, 971:22, 989:15</p> <p>differences ^[7] - 801:5, 837:12, 837:15, 857:12, 858:21, 918:10, 918:11</p> <p>different ^[49] - 673:18, 679:3, 681:17, 681:18, 686:11, 698:3, 698:4, 705:17, 710:18, 740:15, 756:7, 764:23, 788:12, 788:13, 801:23, 802:13, 809:5, 809:6, 834:4, 844:7, 844:20, 858:22, 858:25, 859:1, 879:7, 887:18, 896:22, 908:10, 909:1, 910:3, 914:21, 936:16, 956:15, 957:5, 960:25, 969:24, 970:15, 970:16, 970:21, 970:23, 971:3, 971:16, 986:25, 987:1, 987:3, 988:20, 989:5, 998:23</p> <p>difficult ^[1] - 679:25</p> <p>difficulties ^[1] - 814:15</p> <p>digest ^[1] - 682:24</p> <p>dim ^[7] - 702:20, 850:23, 867:6, 867:25, 868:2, 868:3</p> <p>dimeric ^[3] - 970:19, 970:21, 970:23</p> <p>dinner ^[2] - 1003:18, 1003:19</p> <p>direct ^[33] - 685:2, 689:17, 694:8, 694:21, 831:5, 832:2, 833:7, 839:12, 852:11, 854:21, 855:13, 859:23, 864:17, 866:7, 871:1, 871:4, 873:3, 874:24, 881:15, 882:20, 883:1, 892:19, 905:3, 906:22, 925:16, 928:8, 935:19, 949:7,</p>	<p>949:11, 963:10, 985:11, 989:21, 997:25</p> <p>DIRECT ^[3] - 700:23, 796:7, 895:23</p> <p>directed ^[3] - 817:17, 933:20, 989:21</p> <p>directions ^[1] - 710:18</p> <p>disagree ^[6] - 710:22, 711:22, 761:20, 774:23, 875:20, 942:24</p> <p>disagreeing ^[2] - 875:23, 986:23</p> <p>disagreements ^[1] - 950:20</p> <p>discipline ^[2] - 954:7, 955:1</p> <p>disclose ^[40] - 678:9, 678:11, 678:14, 678:15, 689:8, 690:24, 759:1, 759:6, 759:9, 806:24, 808:11, 808:22, 808:25, 809:2, 809:10, 809:19, 812:14, 812:25, 813:3, 816:8, 816:13, 816:23, 817:7, 818:9, 818:12, 818:16, 818:18, 824:5, 942:18, 942:23, 943:13, 943:14, 944:20, 944:24, 951:4, 952:14, 953:11, 953:17, 956:8, 976:21</p> <p>disclosed ^[40] - 674:10, 674:23, 679:8, 679:11, 679:20, 689:24, 690:15, 690:21, 690:25, 694:9, 694:24, 697:4, 697:8, 697:18, 698:3, 698:16, 759:11, 761:16, 777:2, 788:23, 807:6, 812:20, 817:24, 944:21, 945:16, 946:1, 946:22, 948:3, 952:1, 956:15, 957:5, 957:10, 957:11, 960:18, 960:19, 961:1, 964:15, 972:13, 974:9, 976:5</p>	<p>discloses ^[29] - 674:18, 678:18, 690:5, 697:17, 698:6, 699:2, 773:2, 773:14, 774:22, 812:15, 816:15, 938:13, 940:2, 942:11, 943:11, 943:13, 943:19, 943:22, 944:6, 947:13, 947:14, 947:16, 947:20, 948:10, 952:11, 964:19, 978:19, 999:24</p> <p>disclosing ^[5] - 806:18, 940:8, 959:19, 961:8, 978:2</p> <p>disclosure ^[15] - 674:15, 691:6, 692:25, 694:3, 694:4, 734:8, 739:8, 782:1, 785:1, 785:8, 788:3, 788:6, 811:6, 953:20, 964:1</p> <p>disclosures ^[4] - 803:22, 883:5, 942:20, 980:1</p> <p>discontinue ^[2] - 819:20, 821:24</p> <p>discontinuing ^[2] - 705:3, 820:5</p> <p>discourages ^[3] - 942:19, 943:18, 944:22</p> <p>discovered ^[1] - 718:1</p> <p>discovery ^[2] - 734:15, 759:1</p> <p>discreet ^[2] - 913:10, 914:14</p> <p>discretion ^[1] - 796:21</p> <p>discretionary ^[1] - 693:22</p> <p>discuss ^[8] - 819:9, 945:7, 945:9, 945:16, 945:17, 945:25, 952:3, 992:16</p> <p>discussed ^[15] - 699:4, 722:5, 730:12, 737:7, 815:24, 885:14, 909:9, 910:23, 914:20, 917:9, 925:16, 928:8, 952:15, 997:24, 998:3</p> <p>discusses ^[3] - 805:8, 808:12, 945:5</p> <p>discussing ^[10] -</p>
--	--	--	---	--

<p>723:18, 752:17, 783:23, 799:4, 808:5, 815:5, 822:15, 826:8, 884:10, 941:10 discussion [8] - 774:25, 794:23, 857:17, 915:1, 926:4, 951:23, 952:23, 962:15 Discussion [3] - 927:14, 927:15, 930:6 discussions [1] - 888:21 disease [1] - 783:15 disjointed [1] - 905:20 Disorder [9] - 700:19, 778:19, 783:16, 789:20, 803:21, 816:11, 818:9, 829:9, 931:11 disorder [20] - 704:25, 706:17, 706:19, 708:15, 708:21, 709:6, 720:2, 721:4, 722:7, 723:13, 726:11, 728:1, 729:13, 729:15, 804:12, 805:12, 822:25, 830:15, 844:12, 908:11 Disorders [1] - 918:22 disorders [39] - 700:17, 700:18, 701:19, 702:23, 703:1, 703:7, 706:23, 707:3, 707:15, 708:18, 708:20, 710:5, 712:1, 713:23, 720:23, 722:11, 722:14, 722:19, 724:5, 725:1, 727:24, 729:6, 730:19, 799:17, 799:24, 810:17, 811:3, 811:5, 812:9, 814:14, 815:1, 815:3, 844:8, 844:10, 862:7, 862:16, 882:23, 883:2, 896:23 displaced [1] - 855:1 display [1] - 845:1 displayed [4] - 701:6, 712:21, 791:1, 800:7 dispute [22] - 682:6, 690:9, 690:11, 691:5, 691:21,</p>	<p>700:14, 732:8, 734:10, 734:16, 734:25, 737:17, 739:22, 742:13, 755:21, 761:11, 768:25, 774:16, 776:12, 785:19, 795:4, 946:13, 972:21 disputed [6] - 752:9, 761:21, 761:24, 998:8, 998:10 disputing [1] - 776:4 disruption [1] - 726:10 distinction [1] - 892:18 distinguish [1] - 889:4 distinguished [1] - 702:3 distinguishing [1] - 889:12 DISTRICT [2] - 1:2, 1:3 District [1] - 1004:2 Disturbed [1] - 900:23 dividing [1] - 892:24 DLMO [7] - 867:2, 867:4, 870:8, 877:1, 877:5, 877:12, 884:7 Doctor [8] - 797:16, 842:12, 863:9, 863:22, 881:1, 949:23, 994:5, 1002:2 doctor [7] - 845:7, 850:18, 854:11, 882:1, 903:22, 941:10, 951:20 doctors [2] - 887:10, 889:23 document [129] - 695:13, 697:22, 712:25, 714:2, 714:25, 716:16, 716:22, 717:3, 719:2, 720:6, 721:10, 721:15, 723:20, 724:15, 725:5, 725:8, 726:15, 726:21, 728:10, 728:15, 729:23, 731:4, 731:25, 732:15, 732:23, 733:11, 733:21, 735:17, 735:19, 736:18, 736:25, 737:4, 737:7, 737:24, 738:22, 738:23, 739:1, 739:2, 739:3,</p>	<p>739:5, 739:6, 739:11, 739:12, 740:24, 741:3, 741:7, 741:16, 741:17, 742:20, 743:9, 746:22, 747:9, 749:5, 749:12, 749:21, 750:15, 751:15, 752:1, 752:25, 754:5, 754:17, 754:25, 755:16, 755:18, 756:11, 756:13, 758:7, 760:25, 766:7, 768:15, 770:1, 770:19, 770:24, 772:19, 772:22, 772:23, 774:1, 778:5, 778:8, 778:15, 779:12, 790:4, 791:21, 792:3, 794:12, 794:13, 794:14, 812:10, 826:21, 849:15, 853:5, 860:2, 878:13, 880:17, 880:20, 884:25, 917:13, 918:18, 920:6, 920:7, 921:1, 940:14, 957:16, 963:2, 965:11, 965:13, 966:19, 967:2, 967:4, 967:7, 968:15, 968:16, 968:20, 969:9, 969:14, 973:17, 973:19, 973:22, 975:1, 975:3, 975:5, 975:8, 980:12, 980:14, 983:25, 985:25, 989:18, 991:1, 999:17 document's [1] - 737:12 documents [8] - 696:19, 766:24, 781:20, 791:4, 965:16, 966:15, 973:11, 980:18 dollars [2] - 997:7 dolphins [2] - 890:14, 890:16 domain [3] - 675:25, 691:13, 691:14 done [20] - 681:12, 681:22, 684:12, 684:24, 686:24, 693:15, 693:19,</p>	<p>737:15, 748:15, 757:24, 795:13, 801:20, 834:21, 834:22, 844:18, 879:24, 898:6, 968:7, 985:21 Donuts [1] - 940:4 door [1] - 743:11 dosage [6] - 728:3, 808:17, 833:13, 856:6, 866:21, 923:6 dose [107] - 717:24, 718:3, 718:4, 718:9, 719:17, 723:10, 729:1, 729:3, 729:10, 799:12, 807:2, 807:4, 807:8, 808:15, 812:13, 812:15, 816:13, 818:10, 819:10, 821:5, 823:1, 833:14, 833:15, 833:23, 834:4, 836:3, 837:10, 840:23, 840:24, 841:9, 842:21, 843:4, 845:10, 845:14, 848:8, 848:25, 849:8, 853:16, 853:20, 853:21, 854:6, 856:17, 856:24, 857:2, 870:7, 874:18, 876:15, 876:16, 876:18, 877:11, 877:12, 877:13, 882:22, 883:7, 884:6, 884:7, 884:19, 885:19, 901:14, 901:23, 904:20, 906:16, 907:7, 907:14, 907:15, 907:16, 907:17, 907:19, 909:25, 910:1, 910:9, 911:15, 911:16, 911:19, 911:20, 911:22, 911:23, 912:5, 913:10, 913:14, 913:22, 913:24, 914:2, 914:12, 918:5, 920:5, 920:18, 921:5, 921:7, 921:13, 921:22, 921:24, 922:7, 922:10, 922:13, 922:16, 923:3, 924:2, 924:14, 924:15, 930:8, 933:21,</p>	<p>933:25, 994:13 dose-dependent [1] - 857:2 doses [33] - 723:4, 727:20, 728:24, 729:5, 807:6, 812:18, 842:17, 852:20, 852:23, 853:2, 866:14, 870:16, 873:12, 873:18, 875:4, 875:13, 875:22, 876:1, 876:2, 883:3, 900:3, 909:10, 909:13, 909:20, 910:3, 910:4, 910:11, 914:13, 923:13, 923:14, 924:2, 924:7, 929:24 dosing [3] - 723:8, 806:24, 918:6 double [1] - 912:20 double-plot [1] - 912:20 doubt [6] - 674:9, 723:12, 748:19, 753:19, 797:25, 1002:9 doubts [1] - 1000:18 down [44] - 696:12, 696:14, 718:4, 778:22, 779:23, 780:20, 780:24, 783:18, 786:21, 790:25, 791:6, 791:10, 791:13, 791:24, 792:8, 828:12, 830:20, 836:22, 840:18, 844:23, 845:2, 847:15, 860:17, 863:17, 868:19, 870:21, 872:3, 874:25, 881:9, 893:13, 893:17, 893:18, 923:16, 927:7, 927:14, 929:7, 944:23, 967:11, 988:14, 989:19, 997:19, 1001:6, 1002:16 downside [1] - 1003:15 downstream [1] - 943:1 Dr [222] - 673:14, 674:7, 674:8, 690:19, 691:12, 696:16, 700:12, 700:16, 700:25,</p>
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701:2, 701:3, 702:14, 702:17, 703:3, 703:13, 704:5, 704:9, 704:14, 705:16, 705:21, 710:13, 710:14, 711:2, 711:3, 711:9, 711:23, 713:14, 716:2, 717:21, 718:12, 720:20, 730:24, 731:21, 732:15, 733:9, 735:21, 739:25, 742:4, 746:1, 748:25, 756:14, 765:12, 765:21, 777:19, 777:21, 778:4, 782:5, 782:23, 783:11, 783:20, 784:4, 786:11, 786:24, 787:10, 790:17, 792:10, 793:14, 796:24, 798:11, 798:24, 799:25, 803:7, 809:17, 811:17, 817:14, 818:22, 820:9, 822:5, 825:5, 826:8, 828:4, 829:1, 830:12, 834:25, 839:15, 839:17, 839:20, 839:22, 840:3, 840:6, 849:25, 851:14, 851:24, 855:12, 856:20, 856:23, 860:7, 860:8, 872:18, 873:18, 875:16, 881:17, 882:20, 884:2, 886:2, 886:10, 886:14, 886:23, 886:24, 888:9, 891:14, 894:15, 895:3, 895:5, 895:6, 895:15, 895:25, 896:2, 896:16, 897:12, 897:13, 898:11, 898:19, 898:25, 899:15, 900:11, 901:11, 901:25, 902:1, 902:2, 902:4, 902:11, 903:1, 903:7, 905:23, 906:22, 907:12, 908:4, 909:15, 910:17, 910:23, 910:24, 910:25,	911:10, 914:19, 915:3, 916:1, 917:13, 917:14, 917:15, 917:18, 919:4, 920:8, 924:24, 930:2, 930:23, 935:19, 938:1, 940:18, 940:25, 941:1, 941:19, 941:21, 942:17, 943:11, 944:2, 946:21, 947:3, 947:17, 948:20, 948:21, 948:23, 948:25, 949:13, 949:14, 949:22, 950:2, 950:13, 950:15, 951:13, 952:10, 953:1, 954:11, 954:14, 954:18, 954:21, 955:4, 955:12, 955:15, 956:1, 956:4, 956:7, 956:10, 957:22, 959:18, 959:22, 961:22, 962:3, 963:5, 963:14, 964:9, 965:24, 966:2, 966:17, 966:19, 967:5, 967:24, 968:20, 968:25, 972:19, 973:1, 973:11, 976:12, 976:15, 977:16, 978:12, 978:14, 978:18, 979:6, 979:11, 984:15, 984:17, 984:23 drafts [1] - 935:1 dramatically [2] - 718:5, 885:13 draw [4] - 730:14, 923:1, 963:19, 963:20 drawing [1] - 693:15 Dressman [2] - 934:19, 936:7 drew [1] - 970:17 drift [3] - 708:7, 709:14, 869:19 drifting [1] - 708:10 drive [2] - 707:7, 707:13 drives [1] - 706:19 driving [2] - 704:6, 849:2 dropout [1] - 964:10 dropped [1] - 938:21	drowsiness [1] - 892:9 drowsy [5] - 891:21, 891:23, 892:9, 892:16, 892:17 Drs [1] - 837:13 drug [39] - 703:17, 704:6, 704:11, 704:17, 704:19, 710:12, 730:22, 740:5, 803:21, 803:25, 805:25, 810:9, 813:22, 820:11, 821:25, 831:9, 841:8, 841:11, 846:25, 847:11, 851:11, 881:16, 907:16, 937:20, 937:21, 961:24, 976:23, 985:1, 985:12, 987:16, 991:11, 991:14, 993:14, 995:12, 995:15 drug-driving [1] - 704:6 drug-drug [4] - 704:11, 704:19, 821:25, 881:16 drugs [5] - 709:18, 710:8, 834:8, 862:1, 994:12 DTX [2] - 738:19, 749:9 DTX-073 [1] - 984:21 DTX-154 [3] - 716:6, 716:8, 717:11 DTX-155 [2] - 716:20, 717:12 DTX-156 [2] - 717:1, 717:12 DTX-16 [7] - 729:21, 730:5, 730:9, 812:21, 813:7, 815:6, 872:6 DTX-16.1 [1] - 812:11 DTX-16.7 [2] - 814:7, 873:1 DTX-20 [7] - 797:14, 798:11, 798:18, 798:22, 877:18, 880:11, 893:15 DTX-20.5 [1] - 808:8 DTX-20.6 [3] - 804:5, 806:21, 809:8 DTX-301 [1] - 1002:11 DTX-331 [2] - 934:5, 936:4 DTX-331.2 [1] - 935:4 DTX-331.3 [1] - 934:10	DTX-37 [3] - 723:15, 723:23, 724:2 DTX-39 [5] - 720:4, 720:14, 917:12, 930:22, 931:22 DTX-39.3 [3] - 931:19, 933:1, 933:15 DTX-39.5 [2] - 932:20, 933:11 DTX-41 [6] - 726:13, 726:24, 727:3, 806:10, 876:4, 882:12 DTX-41.10 [2] - 808:19, 823:25 DTX-41.19 [1] - 883:24 DTX-41.2 [1] - 805:15 DTX-41.25 [1] - 807:11 DTX-41.3 [1] - 876:19 DTX-410.1 [1] - 762:16 DTX-411 [2] - 999:8, 999:10 DTX-411.53 [1] - 999:16 DTX-419 [5] - 731:2, 731:12, 749:18, 767:1, 880:16 DTX-419.1 [2] - 738:20, 747:10 DTX-42 [8] - 756:7, 778:5, 793:7, 793:18, 793:21, 794:12, 795:14, 815:16 DTX-42.1 [2] - 793:19, 793:20 DTX-42.10 [1] - 792:4 DTX-42.11 [3] - 780:8, 792:14, 793:1 DTX-42.12 [1] - 793:1 DTX-42.13 [1] - 780:17 DTX-42.16 [1] - 781:5 DTX-42.7 [1] - 793:2 DTX-42.9 [4] - 782:6, 791:1, 793:17, 793:23 DTX-49.2 [2] - 779:10, 787:16 DTX-5.2 [1] - 701:6 DTX-52 [5] - 673:15, 957:14, 958:2, 958:7, 958:9 DTX-55 [1] - 994:3 DTX-555 [1] - 976:20 DTX-73 [1] - 987:5 DTX-73.8 [1] - 989:18 due [3] - 759:2, 759:25, 924:8 duly [1] - 700:21 Dunkin' [1] - 940:3	duration [1] - 855:14 during [10] - 734:14, 867:21, 868:13, 869:3, 869:4, 869:10, 886:18, 890:4, 909:19, 910:23 During [1] - 959:13 dustbin [1] - 688:22
E				
e-mail [7] - 770:1, 934:8, 934:11, 934:18, 935:8, 936:6, 936:16 earliest [4] - 743:1, 744:9, 744:11, 787:11 early [9] - 712:16, 735:17, 760:12, 764:10, 836:9, 838:6, 902:4, 929:2, 957:11 earth [1] - 898:10 ease [1] - 912:20 easier [4] - 672:22, 683:12, 683:13, 796:14 easiest [1] - 981:22 easily [3] - 749:8, 753:18, 760:23 Eastman [2] - 829:16, 837:13 easy [1] - 991:24 ebb [1] - 868:14 edition [3] - 865:3, 865:9, 865:12 editors [1] - 865:15 education [1] - 954:25 educational [2] - 701:20, 896:9 Edward [1] - 958:12 EEG [1] - 890:6 effect [35] - 707:23, 709:24, 711:16, 734:8, 750:5, 810:7, 827:16, 836:16, 837:16, 843:16, 848:5, 848:20, 849:9, 856:17, 857:2, 860:23, 870:17, 871:10, 871:25, 874:13, 883:7, 892:4, 899:20, 907:7, 907:23, 909:5, 910:18, 912:4, 913:2, 913:6, 913:13, 914:11,				

<p>924:8, 932:7, 932:13 effective [27] - 710:24, 719:23, 722:13, 722:18, 722:25, 723:13, 729:5, 799:12, 807:8, 810:16, 811:5, 812:18, 815:3, 825:3, 825:10, 825:25, 827:20, 840:24, 873:12, 876:16, 877:12, 882:23, 884:6, 918:5, 933:21, 935:12, 937:12 effectively [2] - 687:4, 934:1 effects [21] - 683:16, 712:15, 713:17, 713:19, 807:8, 807:9, 826:16, 833:24, 836:3, 841:17, 848:4, 856:24, 865:20, 874:24, 897:2, 907:15, 907:20, 915:11, 924:14, 927:18, 937:21 efficacious [1] - 789:6 Efficacy [2] - 778:17, 789:18 efficacy [1] - 825:14 efficiency [2] - 893:4, 893:7 efficiently [1] - 712:9 effort [3] - 732:15, 811:12, 966:13 efforts [1] - 902:4 either [22] - 683:8, 705:3, 710:5, 831:11, 837:3, 837:17, 854:1, 864:4, 889:22, 889:23, 912:7, 914:6, 916:8, 920:1, 922:10, 924:11, 939:22, 953:2, 953:5, 977:18, 982:19, 996:7 EKINER [1] - 671:15 elaborate [2] - 764:8, 765:6 element [1] - 879:4 elevated [1] - 869:13 elicited [1] - 946:23 elucidation [1] - 679:24 Eluent [1] - 999:19 elutes [1] - 971:10 embodied [1] - 684:12</p>	<p>embodiment [1] - 1000:9 Emens [74] - 700:12, 700:16, 700:25, 701:2, 701:3, 703:13, 710:13, 711:9, 713:14, 716:2, 716:19, 716:25, 717:6, 717:21, 720:20, 730:24, 731:21, 732:15, 733:9, 735:21, 739:25, 742:4, 746:1, 748:25, 756:14, 765:12, 765:21, 777:19, 777:21, 778:4, 782:5, 782:23, 783:11, 783:20, 784:4, 786:11, 786:24, 787:10, 790:17, 792:10, 793:14, 796:24, 798:11, 798:24, 799:25, 803:7, 809:17, 811:17, 818:22, 826:8, 828:4, 829:1, 830:12, 834:25, 855:12, 882:20, 884:2, 886:2, 886:10, 895:6, 900:11, 903:7, 905:23, 906:22, 910:17, 910:23, 910:25, 911:11, 914:19, 915:3, 917:13, 917:18, 919:4, 920:8 EMENS [1] - 700:20 Emens's [3] - 898:11, 898:25, 901:25 empathy [1] - 756:23 employed [2] - 880:4, 932:14 Employed [1] - 959:13 employees [2] - 770:2, 770:3 enclosed [1] - 796:19 end [16] - 685:6, 687:10, 738:16, 746:22, 751:2, 754:17, 792:8, 804:14, 841:16, 847:23, 854:1, 854:5, 887:3, 925:19, 939:17, 996:14 endogenous [13] - 706:4, 706:13,</p>	<p>706:16, 706:19, 708:25, 831:11, 831:14, 831:17, 831:19, 832:8, 868:10, 869:2, 869:16 endogenously [2] - 867:12, 867:14 ends [2] - 757:6, 866:10 engage [2] - 849:2, 1003:16 engineered [4] - 861:18, 862:2, 863:23, 873:19 England [7] - 715:6, 715:24, 840:3, 865:7, 888:12, 891:18, 927:24 English [1] - 865:23 enjoy [1] - 1003:18 enlarge [16] - 835:21, 838:11, 840:19, 843:20, 847:20, 850:11, 851:20, 852:14, 853:7, 855:9, 856:12, 860:2, 860:18, 861:8, 863:6, 873:4 enlarging [1] - 830:10 entered [1] - 968:17 entire [2] - 684:16, 890:6 entitled [3] - 918:20, 959:12, 961:16 entity [2] - 735:10, 740:11 entrain [71] - 702:18, 714:21, 715:23, 718:9, 718:10, 718:15, 723:5, 774:21, 804:13, 810:5, 813:21, 830:22, 832:16, 833:3, 840:11, 840:12, 840:13, 840:14, 844:2, 844:10, 847:9, 851:12, 852:1, 853:21, 863:11, 897:7, 897:10, 899:8, 899:18, 900:4, 901:13, 902:4, 902:12, 903:2, 904:23, 904:24, 907:1, 908:23, 909:14, 909:24, 912:3, 915:13, 915:17, 917:20, 918:10,</p>	<p>919:19, 921:13, 922:8, 922:14, 922:17, 922:25, 923:4, 923:20, 924:4, 924:5, 924:7, 924:8, 924:15, 925:22, 927:9, 927:19, 928:14, 928:21, 929:3, 929:11, 930:9, 932:14, 934:1, 935:10, 937:7 entrained [27] - 708:2, 774:18, 806:1, 846:9, 846:12, 846:17, 852:21, 870:2, 905:2, 906:18, 906:19, 906:21, 908:16, 908:17, 908:20, 908:25, 910:7, 910:8, 910:9, 910:14, 911:15, 911:16, 911:18, 911:20, 921:24, 922:11, 922:22 entraining [15] - 710:24, 718:3, 722:25, 773:11, 773:19, 804:15, 811:25, 838:23, 839:2, 840:24, 846:20, 852:25, 863:13, 877:25, 878:5 Entrainment [1] - 850:17 entrainment [52] - 709:16, 712:19, 719:19, 719:24, 727:19, 774:22, 803:23, 804:3, 805:11, 810:14, 812:7, 813:25, 814:15, 814:17, 818:4, 841:8, 842:23, 843:22, 852:4, 853:15, 854:18, 857:17, 862:20, 862:25, 863:2, 864:2, 864:7, 864:9, 869:11, 870:1, 899:10, 901:16, 901:17, 902:24, 903:9, 906:23, 907:2, 907:4, 908:19, 909:5, 911:23, 911:24, 916:13, 921:10, 923:2, 926:8, 929:12,</p>	<p>930:13, 933:4, 933:22 entry [1] - 779:24 environment [1] - 889:19 environmental [5] - 889:3, 889:6, 889:11, 889:14, 889:20 enzyme [2] - 704:17, 881:4 equivalent [3] - 709:12, 834:5, 834:12 equivocal [2] - 689:6, 691:11 ERIC [1] - 671:9 especially [7] - 718:8, 749:20, 799:23, 811:2, 875:4, 896:20, 990:13 ESQ [14] - 671:3, 671:3, 671:4, 671:4, 671:5, 671:8, 671:9, 671:9, 671:10, 671:12, 671:15, 671:16, 671:16, 671:17 essence [3] - 717:25, 823:19, 860:7 essentially [15] - 687:11, 688:9, 693:3, 694:17, 695:9, 750:8, 751:10, 751:14, 756:7, 759:20, 767:21, 924:9, 970:18, 978:3, 985:1 establish [6] - 679:25, 737:2, 748:4, 759:7, 775:3, 838:3 established [4] - 682:5, 732:11, 748:9, 761:15 establishing [1] - 771:17 estimate [4] - 742:23, 794:7, 794:10, 905:13 et [8] - 1:8, 716:11, 716:19, 716:25, 717:6, 721:14, 935:10, 935:11 etc [2] - 954:17, 977:6 evaluate [1] - 801:1 evaluated [1] - 693:5 evaluation [1] - 842:2 evening [4] - 823:20, 836:9, 869:21, 1003:11</p>
--	---	--	--	--

<p>event [2] - 739:14, 946:16</p> <p>events [1] - 687:21</p> <p>eventually [3] - 765:7, 974:25, 976:9</p> <p>everyday [2] - 921:17, 992:13</p> <p>evidence [110] - 672:21, 679:15, 679:17, 681:18, 682:5, 687:24, 687:25, 691:9, 691:10, 691:18, 712:7, 713:9, 713:12, 714:11, 714:14, 715:11, 715:14, 717:12, 717:15, 717:16, 717:17, 717:18, 719:9, 719:12, 720:15, 720:18, 721:19, 721:22, 722:15, 722:17, 723:24, 724:2, 724:12, 725:16, 725:19, 726:25, 727:3, 728:8, 730:6, 730:9, 731:13, 732:13, 737:9, 737:24, 747:25, 748:10, 756:22, 766:24, 770:17, 771:2, 771:10, 790:4, 790:12, 793:8, 798:19, 798:22, 828:17, 828:20, 828:23, 830:5, 830:8, 850:5, 850:9, 852:8, 854:10, 859:22, 864:24, 872:6, 875:17, 875:18, 875:25, 876:2, 877:18, 880:12, 886:11, 900:15, 901:8, 901:15, 901:16, 902:16, 903:12, 905:3, 906:5, 911:3, 911:7, 917:13, 919:9, 920:2, 920:8, 934:13, 949:3, 958:2, 965:19, 966:16, 968:17, 974:1, 975:12, 976:20, 980:22, 984:1, 984:21, 987:18, 988:18, 998:15, 998:18, 999:1, 1002:12</p>	<p>evidentially [1] - 756:10</p> <p>evidentiary [4] - 673:12, 772:8, 796:11, 938:6</p> <p>evolved [1] - 890:17</p> <p>exact [5] - 673:8, 745:22, 810:11, 818:5, 837:9</p> <p>exactly [27] - 692:11, 694:5, 695:22, 696:7, 723:10, 735:3, 775:21, 776:16, 814:7, 834:13, 837:1, 841:5, 841:10, 842:1, 843:9, 843:19, 847:2, 847:13, 848:15, 851:3, 851:6, 854:7, 869:1, 870:3, 870:13, 878:8, 916:12</p> <p>exam [1] - 989:21</p> <p>examination [30] - 679:16, 689:15, 690:20, 691:12, 691:15, 697:11, 790:14, 797:23, 831:5, 832:2, 833:7, 839:12, 852:11, 855:13, 859:23, 864:17, 866:7, 871:1, 873:3, 882:21, 886:4, 901:25, 906:22, 910:24, 914:20, 928:8, 935:19, 949:8, 949:12, 971:24</p> <p>EXAMINATION [9] - 700:23, 793:12, 796:7, 828:24, 882:18, 895:23, 924:22, 936:1, 984:13</p> <p>examine [1] - 793:10</p> <p>examined [4] - 929:10, 973:7, 973:9</p> <p>examining [2] - 946:18, 946:20</p> <p>example [27] - 676:18, 683:3, 683:14, 696:15, 708:3, 709:7, 710:11, 737:20, 773:22, 797:21, 815:22, 844:16, 848:25, 849:3, 850:19, 864:1, 873:22,</p>	<p>883:12, 890:3, 900:2, 908:19, 910:14, 913:15, 913:23, 914:1, 917:1, 1000:7</p> <p>examples [4] - 706:10, 706:22, 709:21, 710:10</p> <p>except [1] - 692:7</p> <p>excerpt [2] - 907:13, 918:3</p> <p>excerpted [1] - 921:1</p> <p>exchange [1] - 936:6</p> <p>exciting [1] - 715:20</p> <p>exclude [1] - 736:16</p> <p>exclusively [2] - 882:7</p> <p>excuse [3] - 726:20, 736:15, 740:25</p> <p>excused [2] - 736:19, 755:19</p> <p>exercise [1] - 796:20</p> <p>exhibit [22] - 673:12, 690:15, 756:7, 760:2, 762:17, 762:23, 767:4, 770:1, 771:6, 777:4, 777:14, 790:8, 790:12, 793:20, 797:18, 797:24, 876:20, 876:23, 880:9, 902:7, 912:12, 999:7</p> <p>Exhibit [9] - 758:20, 771:7, 795:22, 798:1, 835:10, 843:11, 850:5, 850:8, 999:8</p> <p>exhibits [1] - 859:22</p> <p>exist [1] - 744:2</p> <p>existed [8] - 746:4, 760:9, 760:11, 762:2, 765:19, 789:24, 790:1, 910:12</p> <p>existence [2] - 994:23, 995:4</p> <p>exists [1] - 685:5</p> <p>exogenous [8] - 831:11, 831:16, 831:22, 832:1, 928:13, 928:20, 931:9, 932:2</p> <p>exotic [1] - 990:15</p> <p>expect [9] - 814:18, 827:3, 837:19, 841:9, 948:16, 971:11, 990:11, 990:14, 1002:24</p> <p>expectation [13] - 801:14, 810:23,</p>	<p>811:9, 811:14, 814:9, 878:17, 878:19, 878:25, 879:3, 879:6, 879:13, 978:8, 979:24</p> <p>expectations [1] - 879:10</p> <p>expected [1] - 730:21</p> <p>expensive [1] - 996:18</p> <p>experience [4] - 702:8, 702:11, 702:12, 955:3</p> <p>experienced [1] - 804:22</p> <p>experiments [1] - 835:6</p> <p>expert [69] - 673:21, 673:24, 674:9, 674:17, 677:5, 678:5, 678:22, 679:2, 679:10, 679:19, 679:24, 680:2, 681:18, 689:16, 689:18, 694:3, 694:6, 697:8, 697:17, 697:23, 697:25, 698:2, 699:21, 700:16, 704:5, 704:16, 710:14, 733:15, 733:20, 733:21, 733:22, 734:3, 734:4, 734:7, 734:12, 735:22, 742:5, 756:15, 759:16, 765:13, 781:14, 781:21, 785:1, 785:6, 785:23, 786:4, 788:3, 788:5, 788:7, 790:7, 888:18, 898:19, 938:8, 938:16, 938:25, 940:7, 940:11, 940:17, 943:22, 944:3, 944:5, 944:7, 950:13, 951:7, 956:19, 960:22, 961:10, 964:13, 964:16</p> <p>expert's [2] - 678:1, 697:4</p> <p>expertise [2] - 820:10, 822:6</p> <p>experts [5] - 700:15, 759:14, 802:12, 898:19, 944:13</p> <p>explain [24] - 679:19, 701:6, 707:5,</p>	<p>707:21, 710:1, 735:22, 740:1, 749:22, 763:5, 763:8, 767:17, 768:14, 772:25, 800:7, 801:21, 802:5, 807:17, 810:3, 823:11, 825:22, 883:10, 883:17, 912:19, 946:1</p> <p>explained [8] - 800:19, 800:25, 801:2, 815:20, 815:24, 819:15, 824:11, 824:13</p> <p>explaining [2] - 691:4, 707:3</p> <p>explains [4] - 755:7, 755:9, 914:10, 914:11</p> <p>explanation [5] - 762:20, 785:14, 788:11, 857:1, 883:16</p> <p>explicitly [5] - 772:7, 814:12, 814:14, 943:17, 944:22</p> <p>explore [2] - 881:22, 909:13</p> <p>exposure [2] - 869:21, 869:23</p> <p>extended [2] - 873:25, 874:12</p> <p>extends [1] - 930:12</p> <p>extensive [1] - 971:23</p> <p>extensively [1] - 838:19</p> <p>extent [3] - 688:11, 711:9, 781:19</p> <p>external [1] - 869:14</p> <p>extraordinarily [1] - 688:1</p> <p>extreme [2] - 890:13, 890:20</p> <p>extremely [1] - 710:17</p> <p>eye [1] - 891:19</p>
F				
<p>F.3d [1] - 751:24</p> <p>face [8] - 732:17, 733:25, 735:18, 738:18, 739:6, 740:23, 748:19, 749:23</p> <p>fact [58] - 679:6, 679:10, 679:14, 680:13, 685:14, 688:19, 690:22,</p>				

691:11, 692:18,
692:23, 693:17,
697:16, 697:22,
718:7, 723:2, 726:7,
730:21, 733:8,
734:18, 735:16,
742:10, 748:18,
749:3, 755:23,
758:25, 759:7,
766:16, 767:10,
770:9, 775:5, 776:4,
776:9, 794:9,
797:25, 812:7,
814:18, 829:19,
836:2, 840:23,
842:21, 844:1,
845:8, 845:23,
878:6, 878:18,
878:23, 879:12,
894:11, 899:18,
906:24, 906:25,
917:7, 917:8,
922:14, 935:15,
937:15, 937:19,
938:25
facto [1] - 693:3
factors [2] - 980:3,
980:7
facts [4] - 691:22,
737:3, 755:13, 980:7
factual [4] - 696:24,
736:17, 743:7, 790:6
factually [1] - 755:20
failed [1] - 909:7
fails [1] - 924:5
failure [1] - 951:1
fair [49] - 689:8,
707:14, 739:19,
748:20, 790:11,
833:11, 834:2,
834:17, 835:19,
844:9, 846:19,
849:4, 849:10,
853:21, 854:4,
855:14, 857:20,
858:8, 860:25,
862:20, 863:3,
863:11, 863:12,
864:9, 865:13,
867:22, 868:1,
869:6, 872:21,
874:5, 874:6,
875:19, 878:2,
878:21, 880:5,
880:6, 881:4, 881:5,
881:22, 897:7,
897:13, 905:9,
940:9, 943:23,
945:8, 960:15,
962:16, 987:10,

989:7
fairly [6] - 838:19,
887:22, 909:23,
964:11, 971:23,
978:21
fairness [5] - 695:17,
763:7, 775:15,
796:16, 851:16
fall [2] - 891:24,
891:25
fallen [1] - 892:5
falling [1] - 892:6
familiar [6] - 706:25,
753:13, 834:25,
849:20, 902:2
far [5] - 702:21,
753:17, 818:20,
879:2, 942:7
fast [1] - 676:8
fat [1] - 847:25
faulting [1] - 893:24
FDA [36] - 683:17,
684:5, 684:8,
684:10, 684:11,
685:1, 685:4,
687:17, 687:19,
688:2, 740:5, 740:8,
740:10, 747:5,
752:18, 752:22,
752:23, 757:25,
965:15, 966:22,
969:5, 973:8, 980:8,
981:8, 981:12,
981:24, 982:2,
983:12, 985:5,
986:1, 988:24,
989:8, 989:14,
993:16, 994:22,
995:4
FDA's [2] - 752:19,
982:17
feasible [1] - 683:5
feature [3] - 785:25,
843:25, 844:7
February [8] - 763:14,
765:19, 767:7,
767:9, 767:15,
768:10, 768:23
Federal [6] - 751:23,
751:25, 752:22,
753:9, 753:13, 754:4
federal [3] - 733:7,
740:10, 750:24
federally [1] - 702:24
feet [1] - 682:25
fellow [2] - 702:3,
702:6
fellows [1] - 701:17
felt [1] - 874:3
Ferguson [5] - 721:14,

721:25, 722:6,
722:15, 860:7
few [4] - 703:25,
763:17, 867:14,
898:6
field [28] - 683:22,
700:16, 702:8,
704:4, 708:17,
712:14, 715:21,
829:16, 830:1,
830:2, 833:2,
835:16, 835:18,
836:19, 838:3,
839:25, 842:14,
853:19, 858:16,
859:10, 860:9,
887:11, 887:21,
888:10, 896:24,
897:15, 955:3,
999:21
fields [1] - 700:17
fight [1] - 776:8
Figure [12] - 729:9,
836:1, 836:23,
836:25, 837:9,
861:8, 881:8, 882:2,
919:12, 959:22,
961:25, 963:12
figure [20] - 675:3,
679:9, 682:2, 697:9,
698:25, 738:12,
738:17, 771:12,
827:19, 834:11,
870:22, 870:23,
871:5, 962:1, 962:4,
962:7, 971:5,
977:17, 988:22,
996:21
figures [1] - 881:6
figuring [1] - 796:15
filed [3] - 684:22,
761:11, 948:4
files [1] - 762:24
filing [1] - 699:14
final [5] - 807:13,
882:16, 899:23,
960:3, 963:15
finally [10] - 717:1,
805:6, 808:21,
810:15, 812:24,
817:6, 821:9, 824:8,
847:10, 886:3
fine [4] - 769:1,
776:21, 781:20,
948:18
finish [2] - 833:19,
1002:23
finished [1] - 945:3
firm [1] - 741:22
firms [1] - 742:14

first [94] - 672:8,
678:5, 680:14,
680:16, 687:16,
694:16, 700:21,
701:11, 702:18,
703:25, 704:21,
705:25, 712:17,
712:20, 716:4,
719:23, 723:2,
724:11, 738:25,
739:3, 740:22,
742:3, 742:22,
748:9, 761:10,
761:12, 770:14,
778:14, 779:24,
780:3, 780:6, 782:9,
782:16, 784:21,
785:2, 785:4, 791:8,
792:20, 793:20,
794:2, 800:23,
802:1, 802:2,
803:14, 803:18,
804:9, 805:7,
805:20, 811:24,
818:20, 824:17,
829:5, 829:12,
838:11, 839:14,
839:19, 853:12,
877:13, 896:21,
897:9, 900:4,
901:13, 903:8,
903:23, 904:4,
904:8, 904:10,
904:14, 906:5,
906:8, 909:24,
918:4, 925:20,
925:21, 926:8,
928:12, 929:1,
936:18, 936:24,
943:3, 944:2,
954:23, 957:14,
959:17, 961:20,
963:3, 964:6,
972:10, 974:8,
987:23, 994:11,
994:18, 996:21,
999:17
firsthand [1] - 734:5
five [11] - 728:22,
739:2, 783:20,
852:1, 885:7, 885:9,
885:14, 885:17,
936:12, 961:20,
981:19
five-hour [2] - 885:7,
885:9
five-page [1] - 739:2
fix [1] - 687:7
fixed [1] - 916:4
flip [2] - 778:20,

826:10
flow [2] - 979:1, 979:2
Fluvoxamine [1] -
819:21
focus [8] - 688:12,
811:21, 824:17,
927:16, 934:8,
964:7, 968:2, 999:17
focused [1] - 675:13
folks [2] - 685:3, 863:4
follow [3] - 674:19,
840:12, 994:4
followed [3] - 962:11,
964:4, 990:3
following [6] - 672:3,
678:18, 919:12,
929:13, 982:4,
1003:22
follows [6] - 700:22,
777:22, 788:23,
841:6, 895:22,
951:24
food [28] - 705:8,
823:6, 823:8,
823:13, 823:18,
823:20, 823:21,
823:23, 824:21,
824:23, 825:3,
825:9, 825:11,
825:15, 825:16,
825:25, 826:1,
826:18, 827:16,
827:17, 827:21,
827:24, 828:1,
848:5, 848:20, 849:9
football [3] - 865:19,
865:23, 866:1
FOR [1] - 1:3
force [1] - 702:22
foregoing [1] -
1003:24
forever [1] - 760:17
forget [1] - 992:7
forgive [2] - 905:19,
917:3
forgot [2] - 689:14,
911:2
form [7] - 732:13,
795:2, 842:2,
873:25, 970:21,
981:14, 982:21
format [1] - 746:3
formed [4] - 703:18,
972:4, 972:5, 974:23
forming [18] - 704:1,
704:10, 705:9,
713:5, 714:7, 715:7,
717:8, 719:6,
720:11, 721:15,
723:20, 724:19,

<p>725:12, 726:21, 728:15, 730:3, 797:1, 798:15 Formosa [5] - 688:6, 688:9, 968:7, 968:21, 968:25 formula [1] - 971:13 formulation [2] - 719:17, 918:8 forth [7] - 764:14, 770:22, 771:5, 775:14, 819:14, 819:25, 947:7 forward [7] - 837:3, 837:17, 850:20, 864:20, 906:3, 961:15, 977:16 foundation [14] - 732:1, 748:16, 748:22, 748:25, 771:4, 775:3, 777:3, 777:16, 781:13, 781:24, 781:25, 782:13, 795:14, 958:21 foundational [2] - 733:10, 793:25 four [19] - 717:8, 717:20, 718:12, 729:2, 773:9, 773:18, 826:13, 846:10, 851:25, 861:10, 864:21, 866:21, 870:16, 906:18, 906:24, 908:9, 961:20, 966:25 fourth [3] - 705:5, 807:13, 904:24 fractions [1] - 688:3 framed [1] - 750:4 Frank [3] - 762:21, 765:17, 767:4 Frank-White [3] - 762:21, 765:17, 767:4 frankly [10] - 674:22, 678:19, 686:9, 686:14, 690:8, 691:8, 737:21, 742:13, 759:16, 767:10 free [21] - 708:15, 804:11, 838:23, 844:2, 852:21, 854:22, 888:6, 925:22, 926:9, 926:24, 927:10, 927:19, 928:14, 928:21, 929:3,</p>	<p>929:11, 930:9, 930:13, 932:15, 934:2, 1003:21 free-running [18] - 708:15, 804:11, 838:23, 852:21, 854:22, 925:22, 926:9, 926:24, 927:10, 927:19, 928:14, 928:21, 929:3, 929:11, 930:9, 930:13, 932:15, 934:2 free-standing [1] - 888:6 frequently [1] - 866:3 Friday [1] - 1003:8 friend [1] - 880:16 frivolous [1] - 894:6 front [15] - 681:18, 761:5, 763:11, 774:8, 775:4, 787:17, 791:1, 791:21, 792:3, 793:17, 794:12, 826:12, 897:14, 941:10, 973:4 frustrated [1] - 750:22 full [8] - 681:11, 786:15, 851:20, 851:21, 885:13, 885:17, 890:16, 964:6 fully [1] - 858:5 funded [1] - 702:25 funny [1] - 943:10 furthermore [2] - 761:14, 810:13 furthest [1] - 859:19 Future [1] - 961:17 future [1] - 700:6</p>	<p>generates [2] - 706:6, 706:8 germane [1] - 795:4 gestalt [1] - 879:9 given [18] - 740:21, 744:18, 762:20, 788:4, 789:1, 820:10, 837:10, 841:22, 846:24, 848:25, 895:7, 901:14, 901:23, 904:20, 908:15, 912:24, 914:2, 927:2 gland [1] - 867:21 glean [1] - 679:23 government [18] - 733:7, 738:21, 740:10, 740:11, 745:1, 745:2, 745:3, 745:23, 747:4, 747:5, 747:11, 749:1, 752:2, 754:10, 761:3, 795:10, 795:17, 798:5 grab [1] - 758:9 grade [1] - 683:23 grams [2] - 994:13, 999:20 grant [1] - 936:25 graphically [1] - 836:20 grappling [1] - 790:10 grateful [1] - 894:17 great [5] - 683:11, 705:23, 868:7, 889:1, 894:19 greater [4] - 858:10, 858:11, 994:21, 1000:25 greatly [1] - 857:7 green [7] - 729:9, 807:16, 817:1, 818:14, 821:14, 871:5, 871:21 Greenblatt [2] - 820:9, 894:15 Greenblatt's [5] - 704:5, 704:9, 704:14, 822:5, 881:17 GRETKOWSKI [1] - 671:17 Groombridge [27] - 681:21, 688:12, 689:15, 694:12, 735:25, 738:2, 742:2, 745:6, 746:9, 746:23, 751:5, 751:8, 755:23,</p>	<p>766:2, 771:22, 788:18, 884:2, 884:18, 886:3, 893:20, 893:24, 898:14, 910:23, 911:2, 914:20, 946:20, 947:3 GROOMBRIDGE [200] - 671:8, 673:7, 674:6, 674:24, 675:4, 675:7, 675:11, 675:16, 675:20, 676:8, 676:11, 676:18, 676:21, 677:1, 677:4, 677:8, 677:16, 677:20, 678:15, 679:1, 681:25, 682:15, 682:17, 682:20, 683:2, 684:8, 684:16, 684:21, 685:9, 685:14, 685:17, 686:20, 687:3, 689:10, 689:17, 689:20, 689:22, 690:1, 690:4, 690:13, 691:8, 692:11, 694:13, 694:19, 695:1, 695:3, 695:5, 695:15, 695:22, 696:4, 696:7, 696:9, 696:11, 696:15, 696:18, 697:2, 699:20, 700:1, 700:5, 700:8, 711:17, 713:10, 714:12, 715:12, 717:13, 719:10, 720:16, 721:20, 723:25, 725:17, 727:1, 730:7, 731:14, 731:17, 732:12, 732:20, 732:25, 733:13, 733:18, 733:23, 734:6, 734:10, 734:17, 734:21, 735:4, 735:12, 742:3, 742:22, 743:14, 743:23, 745:7, 745:17, 745:25, 746:10, 746:13, 750:19, 762:7, 763:6, 763:9, 764:5, 764:21, 768:18, 768:21, 769:7, 774:2, 774:13, 774:20, 777:15, 781:12,</p>	<p>781:18, 781:25, 782:12, 784:18, 784:23, 785:7, 787:20, 787:23, 788:2, 788:6, 788:19, 792:21, 793:9, 793:13, 794:19, 794:25, 798:20, 828:8, 828:19, 828:25, 830:4, 830:9, 830:11, 835:9, 835:12, 835:20, 835:22, 836:22, 836:24, 838:10, 838:13, 840:18, 840:21, 844:23, 845:6, 846:3, 846:5, 847:15, 847:16, 847:20, 847:22, 850:4, 850:10, 850:14, 851:19, 851:23, 852:13, 852:15, 853:7, 853:9, 855:9, 855:11, 856:12, 856:14, 860:1, 860:3, 860:17, 860:20, 861:7, 861:9, 863:6, 863:8, 863:17, 863:21, 864:24, 865:1, 866:12, 866:13, 870:21, 870:25, 872:2, 872:7, 872:14, 872:17, 873:4, 873:6, 876:21, 876:25, 880:11, 880:14, 881:20, 881:25, 882:9, 894:2, 894:24, 937:25, 998:11, 998:21, 999:3, 1002:19, 1003:4 Groombridge's [3] - 737:16, 748:7, 956:10 ground [2] - 897:4, 910:19 grounds [2] - 673:19, 751:18 groundwork [1] - 831:8 group [2] - 716:4, 827:24 growth [1] - 861:2 guarantee [1] - 840:14 guess [17] - 672:18, 732:7, 739:12,</p>
	<p>G</p>			
	<p>Gabrielle [1] - 934:19 game [1] - 790:11 GARRISON [1] - 671:8 gather [1] - 771:11 general [7] - 701:7, 703:10, 726:5, 947:2, 947:5, 978:9, 979:25 General [1] - 701:13 generally [7] - 742:14, 830:18, 990:14, 992:1, 992:3, 992:5, 992:11 generate [2] - 962:11, 962:23 generated [1] - 706:4</p>			

<p>741:20, 743:9, 743:11, 752:9, 761:1, 762:19, 782:2, 782:3, 793:16, 826:13, 859:14, 935:1, 947:19 guidance [2] - 677:16, 677:18 Guideline [2] - 918:21, 944:24 guideline [1] - 993:19 guidelines [18] - 683:3, 953:3, 953:5, 953:6, 973:8, 973:9, 976:19, 976:22, 977:4, 977:25, 978:4, 978:11, 978:13, 979:17, 979:19, 980:2, 993:17, 994:9 guy [1] - 757:2 guys [3] - 737:20, 738:7, 766:10 gymnastics [1] - 679:9</p>	<p>821:13, 828:8, 828:10, 828:11, 845:23, 847:24, 874:5, 891:5, 893:7, 893:8, 895:4, 911:24, 937:3, 976:1, 1002:14 half-life [1] - 874:5 halfway [1] - 778:22 halves [1] - 971:4 hand [23] - 707:1, 710:5, 710:6, 747:18, 752:4, 753:8, 753:16, 763:22, 766:7, 777:6, 778:6, 835:21, 840:20, 845:23, 860:19, 884:14, 925:20, 926:3, 930:6, 968:6, 970:12, 970:13, 990:23 handed [3] - 765:23, 786:2, 941:7 handful [1] - 897:14 hanging [2] - 924:8, 936:3 hangs [1] - 912:5 happy [5] - 762:7, 775:12, 796:2, 828:20, 948:6 hard [6] - 834:1, 834:5, 890:11, 935:15, 937:15, 1001:1 Hardeland [37] - 730:2, 730:3, 730:11, 730:14, 730:20, 730:22, 800:17, 811:19, 811:21, 811:24, 812:14, 812:15, 812:18, 812:25, 813:3, 813:4, 813:10, 813:22, 814:4, 814:12, 814:16, 814:18, 814:20, 814:22, 815:4, 818:25, 819:1, 820:2, 820:18, 822:13, 824:4, 872:8, 872:18, 872:24, 873:18, 875:16 Harvard [2] - 702:15, 896:3 hasten [1] - 864:2 hats [1] - 887:19 HCL [1] - 964:4 head [6] - 827:22,</p>	<p>834:24, 892:4, 904:12 head-bobbing [1] - 892:4 head-to-head [2] - 827:22, 834:24 headed [3] - 746:11, 838:14, 963:2 header [3] - 850:12, 959:17, 961:21 heading [4] - 838:12, 863:7, 875:1, 962:6 Health [4] - 701:14, 701:16, 701:25 health [1] - 684:6 healthy [3] - 826:17, 879:24, 885:4 hear [10] - 672:16, 677:23, 678:13, 711:22, 817:16, 825:8, 915:3, 915:6, 954:11, 976:12 heard [13] - 677:7, 682:2, 691:11, 702:20, 704:18, 706:1, 706:12, 708:2, 724:21, 829:19, 832:9, 899:20, 910:7 hearing [4] - 678:5, 839:17, 917:21, 998:23 hearsay [2] - 731:25, 761:2 heart [1] - 706:6 held [6] - 672:3, 686:5, 774:25, 794:23, 951:23, 952:23 hello [2] - 896:2, 924:25 help [12] - 679:10, 687:7, 708:23, 760:15, 765:24, 769:23, 913:12, 940:7, 947:12, 949:6, 950:4, 950:19 helpful [9] - 689:5, 699:21, 758:21, 772:20, 843:5, 947:9, 948:19, 959:2, 959:3 helping [1] - 776:1 helps [1] - 769:20 hemisphere [1] - 890:18 hemispheres [1] - 890:18 hemorrhagic [1] - 900:17 hereby [1] - 1003:24</p>	<p>hereto [1] - 762:22 hesitating [1] - 833:22 Hetlioz [8] - 770:11, 773:1, 778:11, 783:22, 796:25, 815:14, 817:17, 818:8 hide [1] - 868:4 high [21] - 703:14, 704:21, 717:20, 718:4, 727:15, 728:18, 796:19, 799:19, 842:22, 843:4, 847:25, 852:20, 853:2, 854:3, 890:6, 924:3, 924:7, 953:9, 953:18, 964:11, 978:21 high-density [1] - 890:6 high-fat [1] - 847:25 higher [8] - 842:16, 853:21, 853:24, 907:14, 907:17, 912:5, 914:2, 914:3 highest [1] - 978:19 highlighted [32] - 715:25, 720:1, 722:9, 723:3, 725:2, 726:6, 727:20, 729:9, 730:16, 799:10, 799:18, 804:14, 806:17, 806:25, 807:3, 807:14, 808:3, 809:13, 811:1, 812:3, 812:17, 813:6, 814:6, 816:11, 816:14, 816:17, 816:25, 819:8, 821:7, 821:14, 823:15, 968:14 highlighting [2] - 973:4, 981:24 highly [5] - 688:25, 997:20, 997:22, 998:7, 998:8 historic [1] - 798:2 historical [4] - 784:11, 786:13, 786:15, 798:4 Historical [3] - 784:16, 786:6, 786:12 histories [1] - 704:4 history [14] - 688:22, 739:22, 740:17, 744:17, 755:6, 756:8, 767:20,</p>	<p>768:10, 770:21, 838:22, 840:9, 923:18, 965:14, 966:4 History [12] - 741:11, 747:3, 755:7, 785:11, 785:24, 786:14, 786:24, 787:3, 787:9, 787:19, 788:9, 789:14 hits [2] - 831:9, 847:11 hitting [1] - 847:1 hmm [1] - 783:13 HOESCHEN [1] - 671:3 hold [12] - 680:16, 700:9, 747:15, 748:16, 749:12, 752:24, 753:3, 762:5, 767:2, 922:6, 939:2, 951:21 holder [1] - 676:21 Honor [196] - 672:7, 673:7, 674:6, 674:8, 677:21, 677:24, 678:16, 679:23, 680:18, 681:25, 682:21, 683:3, 685:9, 685:25, 686:7, 687:4, 687:14, 689:10, 689:12, 690:8, 690:18, 691:3, 691:8, 691:22, 692:16, 693:18, 694:7, 694:14, 695:15, 695:22, 697:10, 698:10, 698:19, 699:13, 699:20, 700:8, 700:11, 700:13, 712:5, 713:8, 714:10, 715:10, 717:11, 719:8, 719:10, 720:14, 721:18, 723:23, 725:15, 726:24, 727:1, 730:5, 731:12, 731:14, 731:20, 732:4, 732:12, 732:25, 733:6, 733:13, 734:6, 734:17, 734:19, 735:5, 735:13, 735:21, 736:10, 737:5, 739:24, 741:18, 742:3, 743:3, 743:14, 744:1,</p>
H				
<p>h [1] - 963:25 Hack [47] - 719:5, 719:6, 719:14, 719:16, 719:21, 800:15, 800:17, 803:11, 803:15, 804:8, 804:10, 804:21, 805:22, 805:24, 805:25, 809:1, 809:10, 809:18, 810:4, 811:19, 813:11, 813:20, 813:25, 818:25, 819:1, 820:1, 820:3, 820:17, 820:18, 822:12, 822:13, 824:4, 854:13, 856:20, 856:23, 857:5, 905:24, 906:8, 906:14, 908:4, 919:13, 919:23, 928:7, 933:13 hairs [3] - 867:16, 867:20, 868:16 half [24] - 727:21, 728:2, 812:25, 813:1, 816:23, 816:24, 818:12, 818:13, 821:12,</p>				

745:19, 745:25,
746:7, 746:19,
747:7, 748:2,
748:24, 750:19,
752:14, 753:1,
755:2, 756:4, 757:4,
757:20, 758:7,
758:15, 758:20,
762:1, 762:7, 762:9,
763:6, 763:9,
763:15, 764:3,
764:5, 764:21,
766:1, 766:23,
767:18, 768:19,
769:14, 772:18,
774:2, 774:5,
774:13, 775:11,
775:21, 776:9,
776:16, 776:19,
777:1, 777:7,
777:15, 778:1,
781:12, 782:12,
784:18, 785:18,
785:23, 786:3,
787:20, 788:8,
788:19, 790:15,
792:21, 793:7,
793:9, 794:20,
794:25, 795:7,
795:9, 795:23,
796:1, 796:22,
798:9, 798:18,
828:5, 828:8,
828:15, 828:19,
828:22, 830:4,
850:4, 880:12,
881:14, 881:20,
882:11, 886:7,
894:2, 894:14,
894:22, 894:24,
895:14, 895:18,
898:18, 902:17,
904:3, 905:19,
924:17, 924:20,
935:25, 938:5,
939:4, 939:24,
940:25, 941:8,
941:12, 942:6,
943:2, 944:1,
944:12, 946:7,
947:23, 948:2,
948:12, 948:19,
949:1, 951:6, 957:2,
958:4, 959:1,
960:21, 961:2,
961:12, 964:18,
965:20, 972:14,
998:17, 999:3,
1002:20, 1002:21,
1003:5
Honor's [3] - 751:13,

751:21, 761:3
HONORABLE [1] -
1:18
hope [2] - 701:7,
798:7
hopefully [1] - 849:14
hormone [3] - 868:22,
868:24, 897:6
hormones [2] -
706:13, 708:6
hospital [1] - 897:23
Hospital [3] - 702:15,
896:3, 897:20
hour [35] - 727:22,
728:2, 729:11,
729:12, 729:17,
773:3, 773:6,
773:10, 789:2,
812:25, 813:1,
816:24, 817:2,
818:13, 818:15,
821:12, 828:9,
828:10, 828:11,
836:10, 837:5,
841:20, 848:16,
871:12, 871:14,
885:7, 885:9,
885:18, 895:4,
916:8, 927:3,
1002:14
Hour [1] - 700:19
hours [35] - 700:5,
706:9, 708:3,
728:22, 741:23,
772:14, 802:3,
804:23, 804:25,
805:1, 805:2,
808:14, 847:4,
855:18, 855:21,
855:25, 867:11,
867:14, 869:3,
869:4, 869:7,
869:10, 869:20,
871:17, 880:21,
885:14, 885:17,
893:5, 913:16,
916:8, 920:1,
921:12, 921:17,
922:9
housekeeping [2] -
672:6, 828:15
HPLC [15] - 688:7,
968:9, 968:13,
983:16, 983:20,
983:22, 986:11,
986:13, 986:24,
991:14, 991:18,
991:22, 992:9,
992:13, 992:22
human [5] - 726:4,

838:4, 839:3,
840:12, 863:14
humans [1] - 864:5
hurriedly [1] - 759:25
hydride [1] - 964:4
hydrogens [3] -
971:13, 971:15,
971:21
hyperlink [6] - 752:23,
757:13, 767:25,
768:2, 768:15,
783:25
hyperlinks [4] -
740:18, 740:20,
757:13, 767:21
hypnotic [1] - 708:22
hypnotics [1] - 710:6
hypothesis [3] -
687:22, 874:11,
907:23
hypothesized [3] -
841:1, 853:15, 905:5

I

i.e [1] - 797:21
ICH [9] - 944:24,
973:8, 976:19,
978:3, 978:10,
979:18, 980:1,
993:17, 994:8
ICHQ3A [9] - 953:3,
953:5, 976:21,
976:25, 977:21,
977:25, 978:13,
979:16, 993:19
idea [11] - 688:25,
692:24, 767:23,
807:7, 833:15,
853:12, 875:22,
875:24, 890:17,
905:16, 912:4
ideal [1] - 918:6
identical [3] - 795:21,
971:3, 985:2
identification [2] -
682:17, 995:1
identifications [1] -
681:22
identified [20] -
683:21, 684:10,
966:6, 966:8, 968:5,
968:8, 968:9,
968:12, 968:22,
969:6, 969:19,
988:4, 988:5, 989:3,
989:6, 989:23,
990:21, 995:15,
996:2, 996:4
identifier [3] - 778:24,

789:17, 793:3
identifies [1] - 739:7
identify [24] - 677:17,
683:1, 683:5,
687:23, 689:24,
736:4, 950:24,
951:16, 966:12,
966:13, 969:16,
971:20, 972:8,
978:7, 979:22,
983:15, 990:6,
995:5, 995:7,
995:18, 995:22,
996:9, 996:11,
996:15
identifying [8] -
955:23, 978:9,
979:25, 990:12,
993:20, 995:10,
995:16, 995:24
identity [3] - 682:3,
986:14, 986:18
ignorant [1] - 682:23
illicit [1] - 949:8
illustrate [1] - 836:2
illustrating [1] -
908:10
illustration [1] -
912:21
imagine [4] - 693:5,
734:12, 734:14,
735:15
immediately [2] -
870:24, 906:18
impact [2] - 811:8,
916:25
impaired [1] - 821:7
impeach [1] - 767:11
impeached [1] -
695:24
impeachment [1] -
696:1
implications [3] -
825:16, 825:19,
943:1
importance [2] -
774:10, 950:25
important [20] -
692:14, 712:8,
774:10, 774:11,
775:2, 775:13,
814:15, 830:13,
844:1, 846:21,
857:22, 858:7,
867:17, 914:12,
915:16, 940:22,
983:9, 991:11,
998:14, 1002:8
importantly [1] -
706:14

impossible [2] -
696:25, 761:7
impress [1] - 738:9
impression [1] -
686:17
improper [2] - 688:13,
756:13
improve [2] - 728:21,
931:16
improved [1] - 825:14
improvements [2] -
830:23, 832:17
Impurities [25] -
951:16, 953:12,
953:17, 953:19,
966:6, 966:7,
966:12, 968:2,
968:5, 968:8,
968:12, 972:8,
972:24, 976:17,
977:22, 978:6,
978:23, 979:7,
979:21, 981:25,
987:19, 992:7,
992:17, 993:8,
1000:4
impurities [59] -
677:17, 682:18,
683:4, 683:11,
683:18, 684:5,
684:9, 687:23,
688:3, 688:8,
688:23, 693:9,
950:24, 967:10,
968:22, 969:25,
970:4, 974:19,
974:22, 976:4,
976:22, 977:18,
977:20, 978:5,
979:9, 979:20,
979:23, 979:25,
982:4, 982:20,
982:21, 982:22,
982:24, 982:25,
983:8, 983:19,
984:18, 985:12,
986:8, 986:13,
986:14, 987:8,
988:4, 989:15,
989:22, 991:8,
991:10, 991:23,
992:2, 992:10,
993:13, 993:17,
993:20, 993:21,
995:15, 1000:3,
1000:16
impurity [34] - 683:1,
953:12, 953:18,
967:12, 967:13,
967:25, 968:1,

<p>976:16, 977:9, 977:12, 977:13, 985:6, 985:13, 986:15, 986:18, 986:19, 986:20, 988:5, 991:15, 991:18, 993:4, 994:21, 994:23, 994:25, 995:2, 995:4, 995:5, 995:8, 995:11, 995:17, 996:1, 996:22, 997:13, 1000:24 Impurity [15] - 968:10, 968:11, 970:3, 970:14, 987:24, 988:6, 988:8, 988:15, 988:19, 988:20, 988:25, 989:5 IN [2] - 1:2, 1:3 inappropriate [1] - 985:24 inaudible [1] - 814:19 INC [2] - 1:5, 1:8 incapable [1] - 842:22 incentive [2] - 997:9, 997:16 inclined [1] - 697:3 include [4] - 705:2, 826:13, 967:19, 978:15 included [3] - 910:24, 956:16, 957:6 includes [4] - 690:6, 736:25, 746:2, 993:19 including [10] - 700:17, 703:1, 744:20, 744:21, 805:9, 879:8, 901:17, 951:5, 951:14, 952:2 inconsistencies [3] - 899:9, 899:12, 985:19 incorporates [1] - 825:14 increased [1] - 802:18 incumbent [3] - 749:23, 771:1, 775:7 IND [5] - 695:8, 956:12, 967:15, 967:20, 969:7 Indeed [1] - 847:7 indeed [6] - 715:9, 784:12, 787:4, 788:13, 799:5, 876:9 independently [1] - 982:24</p>	<p>indexed [4] - 778:23, 780:15, 781:10, 793:3 indexing [1] - 781:14 indicate [2] - 927:18, 979:3 indicated [4] - 878:19, 966:5, 982:19, 987:21 indicates [1] - 797:20 indicating [1] - 964:10 indicative [1] - 951:1 individual [19] - 687:6, 718:10, 729:18, 841:22, 846:24, 853:1, 908:14, 908:20, 908:24, 909:4, 911:15, 918:10, 918:11, 967:12, 967:25, 982:20, 991:23, 992:10, 1000:24 individualized [1] - 910:4 individually [1] - 716:5 individuals [33] - 702:19, 707:22, 714:20, 715:22, 718:16, 719:19, 719:22, 722:25, 731:11, 797:12, 803:20, 804:11, 806:18, 809:7, 810:6, 813:21, 819:9, 821:4, 821:6, 822:24, 826:17, 830:16, 857:7, 885:4, 892:1, 902:22, 902:25, 904:25, 907:3, 908:9, 910:2, 910:6 induced [1] - 885:6 inducer [1] - 821:25 inducers [1] - 705:3 induces [1] - 773:8 indulge [1] - 890:13 infer [1] - 868:18 inference [1] - 923:1 inferences [1] - 834:3 influence [1] - 696:25 information [24] - 676:16, 692:14, 692:21, 694:24, 712:6, 738:23, 761:16, 766:16, 769:3, 769:4, 785:15, 798:8, 830:18, 850:12, 859:10, 872:15,</p>	<p>872:19, 879:17, 882:1, 924:2, 948:4, 978:4, 978:16, 979:19 informations [1] - 978:10 informed [1] - 989:14 infringe [2] - 818:3, 954:1 infringement [4] - 711:16, 773:8, 800:20, 938:2 infringes [1] - 773:24 infringing [1] - 816:1 inhibition [1] - 862:11 inhibitor [2] - 819:21, 820:5 inhibitors [2] - 705:4, 881:4 initial [4] - 733:6, 789:2, 838:14, 914:4 initiate [1] - 924:12 input [2] - 677:9, 707:24 insomnia [8] - 722:2, 799:2, 808:5, 865:21, 866:19, 879:25, 880:1, 885:6 instance [7] - 679:13, 711:14, 855:17, 865:15, 913:1, 945:17, 945:19 instances [1] - 853:14 instantaneous [1] - 892:10 instead [3] - 760:10, 884:23, 956:4 institution [3] - 839:22, 850:1, 888:5 intake [1] - 995:3 integral [1] - 761:4 intellectual [1] - 677:9 intend [1] - 732:13 intended [3] - 835:17, 862:2, 863:24 intends [1] - 731:22 interact [1] - 889:19 interaction [3] - 704:17, 822:1, 881:16 interactions [4] - 704:6, 704:12, 704:19, 820:11 interest [4] - 887:5, 914:18, 947:7, 1001:5 interested [1] - 887:8 interesting [2] - 718:7, 814:17 interfere [2] - 915:12,</p>	<p>915:20 interim [1] - 693:13 internal [8] - 841:23, 847:1, 847:3, 847:11, 915:4, 916:19, 916:20, 918:11 Internet [10] - 735:6, 735:7, 735:16, 738:20, 738:21, 744:1, 746:18, 749:9, 749:10, 762:24 internship [1] - 701:24 interpret [6] - 679:19, 757:15, 802:6, 940:6, 947:21, 1002:3 interpretation [7] - 680:23, 802:13, 802:15, 802:19, 803:5, 942:25, 1002:2 interpretations [1] - 990:13 interrogatories [1] - 761:13 interrupt [1] - 856:21 Interventions [2] - 791:25, 792:2 interventions [1] - 816:19 intrinsic [1] - 837:6 Intrinsic [1] - 918:21 introduce [6] - 678:25, 700:25, 732:15, 886:10, 896:1, 939:10 introduced [4] - 771:13, 797:18, 797:24, 890:23 introducing [1] - 712:7 introductory [1] - 872:15 inures [1] - 692:1 invalid [12] - 685:19, 685:21, 686:6, 686:10, 688:18, 688:20, 800:14, 818:24, 822:3, 825:20, 881:21, 954:3 invalidated [2] - 938:20, 938:22 invalidity [8] - 685:10, 685:12, 701:10, 759:10, 772:19, 790:22, 818:22, 938:1</p>	<p>invent [4] - 682:14, 682:16, 697:19, 824:16 invented [4] - 682:8, 702:19, 824:16, 825:8 invention [17] - 677:3, 693:1, 766:5, 801:6, 809:25, 810:24, 813:16, 814:10, 824:15, 950:24, 951:2, 955:9, 955:23, 993:1, 993:2, 993:12, 993:16 Invention [3] - 727:9, 826:23, 876:19 inventive [2] - 676:24, 682:25 inventor [17] - 675:22, 676:3, 676:6, 676:15, 682:13, 685:7, 685:11, 685:20, 686:2, 686:8, 686:11, 686:23, 687:6, 824:14, 950:16, 972:7, 972:9 inventors [8] - 684:2, 688:14, 688:16, 692:13, 692:17, 694:22, 765:1, 770:2 inventorship [13] - 678:2, 678:16, 680:5, 681:24, 685:13, 685:25, 686:4, 687:9, 688:13, 948:1, 948:5, 956:6 invested [1] - 811:15 investigated [1] - 866:16 investigator [1] - 897:21 involve [1] - 682:8 involved [4] - 684:1, 741:20, 796:15, 945:20 involving [1] - 926:23 IPD/Information [1] - 792:11 IR,2R)-2-(2,3- dihydrobenzofuran -4-yl)cyclopropane [1] - 945:21 IR,2R)-2-(2,3- dihydrobenzofuran -4-yl)cyclopropyl [1] - 945:23 ironic [1] - 894:1</p>
--	--	--	--	---

<p>irrelevant [6] - 732:10, 732:23, 733:2, 733:4, 738:4, 753:17</p> <p>irreversible [1] - 889:13</p> <p>isolation [2] - 879:15, 885:21</p> <p>issuance [1] - 816:2</p> <p>issue [62] - 672:9, 674:5, 675:7, 679:6, 685:15, 685:24, 686:13, 689:4, 690:23, 691:2, 691:20, 693:20, 694:16, 697:5, 697:19, 699:1, 707:1, 731:20, 734:24, 737:4, 749:4, 749:6, 751:10, 751:22, 755:25, 757:17, 758:6, 758:12, 760:24, 761:24, 769:9, 771:16, 771:18, 772:2, 775:16, 776:16, 785:19, 790:10, 796:13, 796:17, 824:8, 894:9, 938:15, 938:24, 939:5, 940:17, 946:8, 948:3, 948:5, 948:15, 948:20, 949:15, 952:8, 987:19, 987:20, 987:22, 988:2, 990:19, 993:9</p> <p>issued [4] - 684:15, 684:17, 724:18, 726:18</p> <p>issues [12] - 672:16, 672:20, 693:22, 703:14, 711:23, 770:24, 881:16, 887:5, 888:13, 981:15, 1002:17</p> <p>it'd [1] - 732:23</p> <p>it'll [3] - 847:4, 868:4, 868:16</p> <p>item [12] - 718:24, 720:3, 721:5, 726:12, 728:7, 729:19, 730:25, 849:18, 854:8, 877:17, 880:7, 880:15</p> <p>items [3] - 876:7, 880:23, 997:24</p> <p>itself [17] - 720:2, 755:2, 755:7, 767:6,</p>	<p>776:8, 831:15, 831:20, 832:12, 832:16, 848:12, 858:1, 860:15, 861:13, 866:6, 874:4, 879:12, 917:9</p> <p style="text-align: center;">J</p> <p>JACOBS [1] - 671:12</p> <p>January [9] - 705:11, 705:24, 708:16, 709:18, 722:23, 736:7, 809:23, 881:13, 883:6</p> <p>Jazz [1] - 751:23</p> <p>jet [7] - 706:24, 844:16, 844:17, 850:19, 866:2, 866:19, 885:15</p> <p>job [2] - 737:21, 959:4</p> <p>Joe [1] - 891:5</p> <p>JOHN [1] - 671:3</p> <p>join [1] - 948:6</p> <p>joining [1] - 971:2</p> <p>joint [1] - 887:3</p> <p>Jonathan [2] - 700:12, 701:2</p> <p>JONATHAN [1] - 700:20</p> <p>Josephine [4] - 896:15, 896:19, 903:25, 920:10</p> <p>JOSEPHINE [1] - 671:9</p> <p>journal [1] - 865:7</p> <p>Journal [6] - 715:6, 715:25, 840:3, 888:12, 891:18, 927:24</p> <p>journals [1] - 865:9</p> <p>JTX-003 [1] - 880:24</p> <p>JTX-071 [2] - 984:5, 984:8</p> <p>JTX-1 [1] - 774:7</p> <p>JTX-117 [4] - 966:15, 966:20, 969:13, 990:20</p> <p>JTX-12 [1] - 724:13</p> <p>JTX-123 [5] - 716:14, 852:7, 910:20, 911:4, 911:7</p> <p>JTX-127 [1] - 859:14</p> <p>JTX-139 [5] - 712:22, 713:2, 713:8, 713:12, 920:7</p> <p>JTX-146 [12] - 718:25, 719:8, 719:12, 804:19, 805:4, 806:3, 809:14,</p>	<p>854:9, 906:2, 928:6, 928:7, 930:5</p> <p>JTX-147 [6] - 713:25, 714:10, 714:14, 903:13, 925:12, 926:2</p> <p>JTX-148 [5] - 714:24, 715:10, 715:14, 926:14, 927:13</p> <p>JTX-149 [3] - 918:17, 919:6, 919:9</p> <p>JTX-153 [2] - 717:12, 717:18</p> <p>JTX-155 [1] - 717:16</p> <p>JTX-156 [1] - 717:17</p> <p>JTX-246 [1] - 928:25</p> <p>JTX-39 [1] - 720:18</p> <p>JTX-5 [4] - 826:3, 826:7, 828:16, 828:23</p> <p>JTX-91 [3] - 725:6, 725:15, 725:19</p> <p>JTX-94 [4] - 721:7, 721:12, 721:18, 859:17</p> <p>JTX-94 [1] - 721:22</p> <p>JTX-DTX-154 [1] - 717:15</p> <p>Judge [1] - 1:18</p> <p>judge's [1] - 693:23</p> <p>judicial [5] - 733:8, 755:2, 755:11, 755:13, 795:24</p> <p>July [55] - 733:9, 735:23, 738:24, 740:18, 740:24, 740:25, 741:11, 742:21, 745:14, 745:24, 747:2, 747:13, 748:1, 748:14, 748:21, 749:6, 749:19, 750:10, 754:11, 754:15, 754:20, 754:24, 754:25, 755:19, 756:1, 759:1, 759:21, 760:9, 767:23, 767:25, 771:18, 772:17, 773:14, 776:15, 779:22, 780:2, 780:5, 780:7, 782:9, 785:10, 787:12, 787:19, 788:24, 789:13, 789:20, 789:24, 790:2, 790:5, 790:9, 790:20, 791:9, 791:12, 794:5, 795:12, 796:25</p>	<p>jumping [1] - 872:5</p> <p>June [4] - 761:11, 770:23, 934:18, 935:5</p> <p style="text-align: center;">K</p> <p>KAREN [1] - 671:12</p> <p>KAUN [1] - 671:15</p> <p>keep [6] - 849:13, 893:17, 921:21, 958:17, 993:4, 995:17</p> <p>keeping [1] - 869:16</p> <p>keeps [1] - 909:6</p> <p>KELLER [1] - 671:2</p> <p>kept [1] - 693:6</p> <p>KERRY [1] - 671:16</p> <p>kind [26] - 677:18, 722:12, 737:14, 737:15, 750:22, 758:12, 768:13, 772:9, 810:25, 812:7, 827:23, 833:15, 834:1, 834:5, 835:15, 843:5, 863:22, 868:6, 868:8, 874:23, 879:8, 879:9, 887:18, 892:18, 986:5, 986:11</p> <p>KLEIN [1] - 671:10</p> <p>knowing [10] - 682:8, 683:10, 683:23, 905:11, 977:5, 977:13, 977:18, 982:23, 986:18</p> <p>knowledge [2] - 775:14, 835:16</p> <p>known [32] - 676:12, 699:4, 699:5, 709:18, 710:18, 722:9, 722:22, 829:16, 830:1, 840:10, 853:19, 853:24, 857:6, 859:10, 863:23, 865:6, 881:13, 882:2, 882:6, 883:18, 892:3, 896:24, 955:18, 974:20, 974:22, 976:6, 979:2, 986:14, 991:6, 991:10, 991:22, 997:21</p> <p>knows [1] - 735:22</p>	<p style="text-align: center;">L</p> <p>lab [4] - 886:18, 919:22, 930:19, 930:20</p> <p>label [4] - 773:7, 817:17, 818:2, 818:8</p> <p>labeled [4] - 747:10, 965:8, 973:16, 980:11</p> <p>labels [1] - 773:5</p> <p>laboratory [5] - 702:14, 702:17, 887:3, 909:15, 909:16</p> <p>lack [7] - 685:13, 691:25, 731:25, 750:17, 825:20, 857:1, 860:22</p> <p>lag [9] - 706:25, 844:16, 844:17, 850:19, 866:2, 866:19, 885:15, 908:20, 908:23</p> <p>LAH [1] - 964:3</p> <p>laid [3] - 691:22, 778:4, 795:13</p> <p>Lancelot [1] - 746:14</p> <p>Lancet [8] - 754:18, 779:7, 780:16, 793:6, 864:15, 864:21, 865:3, 865:6</p> <p>language [5] - 797:19, 824:18, 885:9, 998:6, 1002:10</p> <p>Lankford [38] - 798:14, 798:15, 798:25, 799:1, 799:3, 799:16, 799:18, 800:15, 803:11, 803:15, 803:17, 803:18, 803:19, 803:22, 806:15, 806:16, 806:17, 807:22, 807:25, 808:1, 809:1, 809:2, 809:3, 809:18, 810:8, 810:25, 811:2, 818:25, 820:1, 820:3, 820:16, 822:12, 824:3, 877:18, 878:1, 878:9, 879:8, 880:3</p> <p>Lankford's [1] - 811:6</p> <p>large [4] - 900:1, 917:3, 961:23, 996:24</p> <p>large-scale [2] - 900:1, 917:3</p>
--	---	---	--	--

<p>larger [3] - 840:23, 853:15, 913:24</p> <p>laser [1] - 912:25</p> <p>last [41] - 676:9, 699:25, 700:1, 721:5, 724:21, 741:23, 741:25, 745:13, 759:3, 760:18, 763:14, 767:7, 780:25, 783:23, 791:10, 811:20, 822:7, 824:8, 840:19, 845:23, 847:21, 853:7, 882:5, 903:22, 903:25, 904:5, 904:8, 904:11, 905:21, 914:3, 918:18, 920:6, 920:7, 923:22, 964:7, 964:8, 974:16, 980:10, 983:11, 989:19, 999:16</p> <p>lasted [1] - 913:15</p> <p>lasts [1] - 673:4</p> <p>late [6] - 690:16, 691:6, 745:14, 760:12, 844:13, 936:25</p> <p>latency [1] - 875:3</p> <p>latest [1] - 745:15</p> <p>launch [1] - 673:2</p> <p>launched [2] - 684:23, 751:5</p> <p>law [3] - 676:3, 692:16, 796:18</p> <p>lawsuit [1] - 880:25</p> <p>lawyers [4] - 737:1, 764:19, 800:19, 824:11</p> <p>lay [13] - 742:10, 748:16, 748:22, 771:3, 771:24, 775:3, 777:3, 777:16, 824:13, 831:8, 868:7, 912:13</p> <p>laying [1] - 748:25</p> <p>LC/MS [5] - 969:7, 971:6, 971:9, 989:23, 989:25</p> <p>LC/NMR [3] - 971:17, 989:23, 990:3</p> <p>lead [4] - 677:6, 718:13, 817:18, 985:22</p> <p>leads [1] - 937:11</p> <p>learned [3] - 690:9, 690:22, 865:10</p> <p>least [16] - 673:4,</p>	<p>674:9, 682:11, 739:3, 739:12, 771:8, 807:9, 848:24, 858:18, 862:6, 890:4, 892:1, 942:8, 954:8, 955:11, 955:25</p> <p>leave [2] - 936:3, 996:11</p> <p>lectern [1] - 775:25</p> <p>led [3] - 904:11, 935:11</p> <p>left [26] - 730:17, 736:19, 738:21, 738:25, 747:18, 753:8, 799:10, 808:4, 809:13, 810:4, 811:1, 813:6, 814:22, 816:14, 817:1, 821:4, 835:21, 845:23, 861:13, 873:5, 900:17, 938:5, 941:17, 969:18, 970:12, 990:23</p> <p>left-hand [6] - 747:18, 753:8, 835:21, 845:23, 970:12, 990:23</p> <p>legal [5] - 672:20, 698:3, 774:16, 800:24, 948:3</p> <p>legend [2] - 962:2, 963:13</p> <p>legitimate [1] - 743:6</p> <p>length [3] - 708:3, 869:20, 985:20</p> <p>less [16] - 764:6, 764:12, 840:23, 859:4, 859:8, 868:22, 907:24, 963:15, 972:24, 979:20, 979:23, 983:7, 994:13, 1000:5, 1000:15</p> <p>letter [5] - 963:23, 980:15, 981:6, 981:11, 982:18</p> <p>letters [1] - 980:8</p> <p>letting [1] - 981:8</p> <p>level [13] - 703:14, 704:21, 717:20, 727:15, 728:18, 801:4, 868:10, 894:10, 894:11, 953:9, 985:13, 1000:3</p> <p>levels [4] - 866:21, 868:4, 868:19, 869:13</p>	<p>Lewy [22] - 702:17, 702:19, 715:21, 716:11, 716:19, 716:25, 717:6, 717:21, 718:12, 842:9, 842:11, 849:25, 887:2, 887:7, 910:24, 911:11, 912:2, 929:7, 929:25, 930:2, 930:17</p> <p>Lewy's [1] - 909:15</p> <p>liberty [1] - 895:18</p> <p>licensed [2] - 687:4, 925:6</p> <p>life [1] - 874:5</p> <p>lifestyle [2] - 915:12, 915:20</p> <p>light [24] - 702:20, 707:24, 740:2, 801:10, 809:5, 819:23, 821:7, 821:17, 822:3, 850:24, 867:19, 867:25, 868:2, 868:3, 869:11, 869:15, 869:16, 869:21, 869:23, 897:2, 898:7, 945:14</p> <p>light-perception [1] - 821:7</p> <p>lights [2] - 867:6, 867:15</p> <p>likelihood [3] - 823:17, 953:15, 953:22</p> <p>likely [5] - 823:17, 823:22, 828:2, 841:16, 853:16</p> <p>likewise [1] - 876:10</p> <p>limitation [33] - 802:1, 802:2, 803:14, 803:18, 804:9, 805:7, 805:18, 805:20, 806:6, 806:12, 806:14, 806:24, 807:15, 807:24, 808:25, 809:2, 809:11, 809:19, 811:25, 812:14, 812:24, 813:12, 815:21, 816:9, 816:22, 819:23, 820:4, 820:7, 822:3, 823:7, 824:5, 944:25</p> <p>limitations [15] - 773:12, 773:16, 801:18, 801:23, 807:20, 813:3,</p>	<p>816:5, 817:23, 819:4, 819:11, 821:15, 821:16, 874:4, 1000:10, 1000:12</p> <p>limited [6] - 711:10, 711:12, 737:23, 738:8, 922:13, 967:25</p> <p>limiting [1] - 991:10</p> <p>line [13] - 780:25, 845:23, 855:14, 882:21, 884:5, 908:16, 909:1, 923:10, 936:7, 970:17, 970:24, 989:20, 999:18</p> <p>lines [6] - 675:8, 853:8, 866:11, 892:15, 944:23, 961:20</p> <p>link [3] - 786:14, 798:2, 798:3</p> <p>links [2] - 788:12, 792:11</p> <p>liquid [2] - 989:25, 990:3</p> <p>Lisa [1] - 906:8</p> <p>list [5] - 673:13, 760:2, 767:21, 770:1</p> <p>listed [8] - 716:3, 734:23, 779:21, 780:1, 792:25, 977:4, 1000:16</p> <p>listen [2] - 682:24, 697:24</p> <p>listened [2] - 677:18, 751:6</p> <p>listening [2] - 772:14, 950:10</p> <p>listing [1] - 966:3</p> <p>literally [1] - 755:8</p> <p>literature [8] - 683:19, 704:4, 708:13, 720:22, 730:15, 837:24, 899:17, 922:3</p> <p>lithium [1] - 964:4</p> <p>live [4] - 775:16, 783:3, 890:15</p> <p>living [1] - 849:2</p> <p>LLP [3] - 671:2, 671:8, 671:12</p> <p>LNA [1] - 875:3</p> <p>local [1] - 890:5</p> <p>locations [1] - 808:12</p> <p>lock [2] - 908:17, 908:22</p> <p>Lockley [41] - 711:3, 711:23, 714:5,</p>	<p>714:16, 780:12, 780:14, 781:7, 781:9, 792:15, 792:18, 792:25, 793:1, 839:15, 839:17, 856:20, 895:3, 895:5, 895:15, 895:25, 896:2, 898:19, 899:15, 901:11, 903:1, 903:19, 904:13, 906:14, 907:12, 908:4, 908:5, 911:10, 916:1, 919:13, 919:23, 924:24, 929:17, 932:21, 933:12, 935:10, 935:19</p> <p>LOCKLEY [1] - 895:21</p> <p>Lockley's [2] - 710:14, 840:6</p> <p>lodged [1] - 893:25</p> <p>logs [2] - 740:15, 747:7</p> <p>London [1] - 885:15</p> <p>long-term [1] - 907:15</p> <p>longest [3] - 818:20, 922:3, 922:9</p> <p>look [90] - 678:21, 680:4, 683:14, 692:3, 698:14, 698:15, 700:4, 712:20, 724:11, 736:4, 736:20, 736:22, 746:22, 752:3, 752:12, 752:16, 753:5, 753:14, 754:25, 755:11, 768:7, 768:22, 780:10, 780:24, 787:16, 790:25, 791:3, 791:19, 797:8, 807:13, 816:6, 822:18, 838:10, 844:6, 844:16, 845:22, 847:17, 849:15, 851:16, 856:11, 857:1, 863:4, 863:16, 863:19, 866:6, 870:20, 873:2, 874:25, 881:6, 883:11, 884:25, 890:7, 890:14, 892:5, 899:14, 902:7, 903:13, 906:2, 913:9, 915:25, 918:17,</p>
---	--	--	---	--

920:6, 920:17,
925:19, 926:3,
926:21, 927:14,
928:12, 929:1,
929:6, 930:5,
931:19, 933:15,
938:7, 939:5,
941:25, 943:6,
948:7, 955:22,
957:13, 959:11,
968:6, 968:15,
969:11, 987:23,
989:20, 990:20,
994:1, 1002:10
looked [20] - 699:21,
704:3, 742:6,
744:18, 757:14,
758:3, 767:9,
767:15, 768:1,
772:16, 785:17,
786:19, 790:5,
790:9, 849:21,
870:16, 871:19,
957:23, 980:8,
988:19

looking [46] - 736:5,

745:19, 763:10,
774:4, 779:12,
789:5, 790:18,
792:16, 795:3,
795:9, 797:15,
799:14, 806:20,
813:4, 815:14,
816:19, 819:7,
820:23, 840:9,
845:1, 845:2,
856:25, 859:18,
866:18, 870:4,
870:24, 874:21,
876:19, 881:8,
884:14, 885:20,
890:6, 890:9,
894:11, 897:1,
906:13, 908:8,
909:19, 911:13,
918:1, 924:13,
931:23, 969:9,
971:21, 987:16
looks [11] - 740:21,
768:24, 779:3,
795:19, 801:20,
807:14, 808:18,
890:10, 912:13,
936:23, 943:6

lose [1] - 895:19

loses [1] - 921:8

lost [3] - 676:10,

707:24, 744:15

low [11] - 718:3,

719:17, 852:20,

852:23, 854:2,
854:6, 868:14,
924:3, 930:8,
978:25, 979:2
low-dose [1] - 930:8

lower [25] - 729:5,

835:21, 848:24,

853:20, 853:25,

854:1, 855:10,

856:13, 863:20,

875:13, 875:18,

875:22, 876:1,

876:2, 907:14,

907:16, 907:19,

909:10, 909:13,

909:19, 911:16,

913:22, 969:18,

990:22, 995:3

lowest [5] - 807:7,

876:16, 877:12,

884:6, 994:11

LPS [1] - 875:3

lunch [2] - 828:7,

1002:23

LV/NMR [1] - 969:7

M

MA-1 [6] - 727:10,

727:13, 807:1,

808:13, 823:15,

877:8

machine [1] - 992:19

Machine [16] - 734:22,

735:1, 735:3, 735:4,

742:24, 742:25,

743:4, 743:13,

743:17, 743:25,

744:10, 760:7,

760:8, 768:8, 776:4,

776:11

magnetic [1] - 990:4

magnitude [3] -

883:17, 883:21,

927:19

mail [7] - 770:1, 934:8,

934:11, 934:18,

935:8, 936:6, 936:16

main [4] - 717:25,

867:18, 891:12,

916:2

mainstream [1] -

990:16

maintain [1] - 938:13

maintained [3] -

747:11, 785:16,

798:5

maintaining [5] -

773:12, 773:19,

805:19, 806:6, 806:9

maintains [1] - 735:11

maintenance [1] -
844:21

major [1] - 888:4

majority [2] - 892:23,

964:12

mammals [1] - 890:14

Man [1] - 900:23

manage [1] - 683:19

manmade [2] -

724:10, 861:18

manufacture [2] -

952:1, 996:22

manufactured [1] -

832:14

manufacturer [3] -

951:4, 980:16,

991:14

manufacturers [6] -

677:10, 677:11,

688:6, 984:25,

985:7, 986:8

manufacturing [3] -

950:25, 963:9,

966:21

map [1] - 881:8

March [14] - 1:14,

738:13, 742:25,

744:7, 744:11,

762:3, 762:12,

763:20, 763:22,

764:1, 765:18,

765:19, 767:5,

776:11

marine [1] - 890:14

marked [1] - 762:16

marker [2] - 868:8,

868:22

markers [3] - 901:17,

925:24, 926:10

market [3] - 684:14,

684:18, 684:19

Marlene [1] - 934:19

mass [3] - 971:9,

971:11, 989:25

Massachusetts [1] -

701:23

master [1] - 836:13

master's [1] - 955:2

match [1] - 744:14

matched [1] - 827:25

matches [1] - 841:24

material [3] - 712:8,

757:5, 894:3

materials [3] - 682:3,

703:7, 753:23

mathematics [1] -

677:15

matter [12] - 686:14,

696:24, 698:7,

732:22, 733:7,
748:11, 761:1,
790:1, 828:16,
848:17, 916:21,
940:3

Matters [2] - 758:8,

758:11

matters [5] - 672:6,

672:8, 841:7,

841:11, 915:4

maximum [1] - 994:13

MCTIGUE [1] - 671:16

meal [1] - 847:25

mean [78] - 672:13,

676:15, 678:23,

682:22, 684:21,

687:8, 690:12,

691:12, 692:3,

693:22, 694:1,

695:17, 695:19,

696:13, 696:23,

723:9, 724:9,

732:10, 732:18,

737:14, 744:25,

750:3, 750:20,

750:21, 750:23,

751:4, 753:18,

755:11, 760:25,

761:23, 764:19,

768:16, 772:10,

775:16, 783:3,

785:14, 786:8,

805:11, 810:25,

811:10, 815:19,

823:19, 824:12,

826:12, 831:9,

832:7, 832:12,

834:2, 838:5, 844:7,

844:10, 855:18,

855:20, 856:21,

858:9, 878:2,

883:11, 887:6,

887:23, 888:11,

888:21, 889:23,

891:1, 893:1,

897:23, 939:13,

939:15, 943:5,

943:6, 944:21,

945:6, 948:10,

958:21, 989:12,

997:12, 1000:12,

1000:13, 1003:2

meaning [9] - 706:4,

727:18, 802:20,

802:25, 814:19,

837:6, 891:10,

921:5, 921:12

meaningful [1] - 833:9

means [21] - 733:3,

757:6, 757:23,

764:7, 802:8,
823:13, 831:11,
832:13, 835:23,
867:9, 867:20,
870:2, 877:9,
878:25, 892:8,
932:8, 943:13,
946:2, 954:1,
994:21, 995:7
measure [9] - 789:3,
789:9, 842:5,
850:22, 891:20,
893:4, 905:12,
905:17, 984:25

measured [5] - 789:4,

891:18, 901:16,

914:22, 922:2

measurements [2] -

901:18, 901:21

measuring [3] -

870:11, 891:13,

892:5

mechanical [1] -

773:14

mechanism [7] -

709:16, 709:24,

710:1, 804:2,

805:11, 810:11,

812:6

mechanisms [1] -

860:22

medical [6] - 701:23,

865:6, 886:14,

886:17, 886:18,

925:1

Medical [2] - 702:15,

896:3

medication [3] -

708:23, 708:24,

925:7

medicine [5] - 803:2,

887:2, 887:16,

887:20, 887:22

Medicine [10] -

701:17, 702:7,

702:24, 715:6,

715:25, 723:2,

723:17, 840:4,

888:12, 927:24

Medicine's [1] -

703:11

meet [4] - 685:15,

737:7, 764:8, 765:6

meet-and-confer [1] -

765:6

<p>730:21</p> <p>Melatonin [3] -</p> <p>838:15, 850:16, 900:23</p> <p>melatonin [231] -</p> <p>702:18, 702:20, 706:13, 709:22, 710:2, 710:19, 710:23, 711:25, 712:12, 712:15, 712:17, 713:17, 713:20, 714:19, 715:22, 717:23, 718:2, 718:14, 719:18, 719:22, 720:23, 721:2, 721:5, 722:1, 722:3, 722:5, 722:6, 722:10, 722:16, 722:17, 722:20, 722:22, 722:24, 723:4, 723:8, 723:13, 724:5, 724:8, 726:8, 727:17, 789:10, 797:9, 799:21, 804:25, 810:5, 810:6, 810:10, 812:4, 813:21, 813:23, 813:24, 814:1, 814:19, 830:21, 831:4, 831:6, 831:14, 831:15, 831:16, 831:19, 831:20, 831:22, 831:23, 832:1, 832:5, 832:6, 832:8, 832:10, 832:12, 832:13, 832:16, 832:23, 833:8, 833:14, 833:25, 834:19, 835:1, 836:3, 836:8, 836:15, 837:2, 838:3, 838:8, 838:23, 840:23, 841:2, 842:17, 843:1, 843:23, 847:9, 848:25, 849:13, 850:24, 852:21, 853:16, 855:20, 856:7, 857:6, 857:9, 857:10, 857:13, 857:15, 857:16, 857:21, 857:25, 858:1, 858:22, 859:7, 860:14, 860:15, 860:23, 861:1, 861:13, 861:19, 862:10,</p>	<p>863:24, 865:20, 867:6, 867:12, 867:14, 867:22, 868:1, 868:2, 868:4, 868:5, 868:10, 868:19, 868:21, 869:2, 869:12, 869:17, 873:20, 874:1, 874:4, 882:6, 896:21, 896:22, 897:5, 897:10, 898:15, 899:8, 899:18, 900:3, 900:5, 900:11, 901:14, 901:17, 901:20, 902:5, 902:12, 902:23, 903:9, 904:19, 904:20, 904:22, 905:1, 905:5, 906:16, 907:14, 907:19, 908:13, 908:16, 909:5, 909:11, 909:14, 909:20, 910:12, 910:15, 911:16, 912:5, 912:25, 913:5, 913:15, 913:18, 914:5, 914:12, 914:21, 915:11, 915:23, 916:12, 917:8, 917:9, 917:19, 918:8, 918:12, 918:14, 919:18, 919:25, 920:5, 920:19, 921:6, 921:17, 922:23, 923:6, 923:18, 923:19, 924:1, 924:2, 924:7, 924:14, 925:22, 926:9, 927:3, 927:8, 927:18, 928:13, 928:20, 929:3, 929:11, 929:13, 930:8, 930:14, 931:10, 931:14, 932:2, 932:14, 933:4, 933:5, 933:21, 933:25, 935:9, 937:7, 965:4</p> <p>melatonin's [2] -</p> <p>722:8, 932:7</p> <p>melatonins [1] -</p> <p>850:25</p> <p>melting [2] - 978:24, 978:25</p> <p>member [3] - 702:1, 702:5, 702:7</p>	<p>memorializes [1] -</p> <p>790:5</p> <p>men [1] - 904:19</p> <p>Mental [1] - 701:13</p> <p>mental [1] - 679:9</p> <p>mention [14] - 775:18, 775:19, 855:5, 864:8, 872:23, 876:11, 877:25, 946:3, 946:4, 946:5, 953:13, 953:18, 979:7, 979:8</p> <p>mentioned [15] -</p> <p>703:2, 710:4, 720:20, 721:24, 771:6, 773:18, 798:24, 811:19, 839:5, 867:4, 871:1, 876:5, 878:5, 910:17, 911:14</p> <p>mentioning [1] - 962:6</p> <p>mentions [3] - 864:7, 864:10, 978:15</p> <p>mentor [1] - 917:15</p> <p>mere [2] - 878:23, 879:12</p> <p>merely [2] - 734:7, 840:10</p> <p>merits [1] - 751:22</p> <p>met [3] - 780:4, 886:14, 886:16</p> <p>metabolic [1] - 881:9</p> <p>metabolism [1] -</p> <p>726:2</p> <p>metabolized [2] -</p> <p>874:8, 882:7</p> <p>methanamine [1] -</p> <p>945:24</p> <p>methenamine [11] -</p> <p>675:13, 690:7, 960:5, 960:6, 960:15, 962:11, 962:17, 962:22, 963:20, 1001:16, 1001:21</p> <p>method [10] - 704:11, 704:24, 705:2, 705:7, 773:8, 825:9, 962:5, 974:20, 982:20, 982:21</p> <p>Methods [2] - 884:25, 926:21</p> <p>methods [10] - 724:25, 883:1, 951:4, 951:5, 951:14, 952:1, 952:2, 956:15, 957:5, 964:25</p> <p>Michele [2] - 1:24, 1004:2</p> <p>middle [2] - 857:2,</p>	<p>912:1</p> <p>might [51] - 672:13, 672:22, 673:1, 693:21, 695:14, 723:11, 736:17, 737:5, 739:12, 740:2, 743:6, 744:6, 749:22, 755:20, 756:19, 833:8, 838:8, 845:9, 848:7, 849:7, 853:22, 856:8, 857:11, 874:12, 875:22, 890:8, 890:18, 891:24, 892:3, 892:5, 892:10, 897:4, 907:7, 907:19, 907:25, 935:12, 937:12, 937:18, 940:11, 940:14, 952:5, 968:10, 972:1, 972:3, 972:5, 977:5, 977:6, 977:12, 979:3, 979:4, 997:2</p> <p>milligram [5] - 834:5, 904:20, 910:9, 911:24, 995:2</p> <p>milligrams [83] -</p> <p>719:18, 719:22, 723:5, 727:21, 728:3, 728:25, 729:10, 773:2, 773:5, 773:10, 788:24, 797:5, 799:12, 806:13, 806:20, 807:2, 807:4, 807:5, 816:7, 816:15, 819:10, 823:2, 833:14, 834:15, 834:16, 837:14, 845:9, 845:13, 852:23, 852:25, 853:3, 866:23, 866:24, 870:5, 870:6, 870:18, 871:7, 871:25, 873:13, 873:23, 874:19, 874:21, 875:4, 875:9, 875:17, 876:18, 882:22, 883:3, 883:8, 883:12, 883:13, 883:18, 884:18, 901:24, 902:22, 910:5, 910:8, 910:14, 911:17, 911:22, 912:3, 921:8, 923:14, 923:15, 923:19,</p>	<p>924:3, 924:6, 927:3, 928:14, 928:21, 929:14, 929:20, 930:8, 930:14, 934:1</p> <p>MILLIKEN [198] -</p> <p>671:5, 700:11, 700:24, 711:8, 711:15, 711:21, 712:5, 712:11, 713:8, 713:13, 714:10, 714:15, 715:10, 715:15, 717:11, 717:19, 718:23, 719:8, 719:13, 720:14, 720:19, 721:18, 721:23, 723:23, 724:3, 725:15, 725:20, 726:24, 727:4, 730:5, 730:10, 731:12, 732:4, 732:6, 733:6, 733:16, 735:21, 736:2, 736:6, 736:10, 736:13, 737:5, 738:15, 739:10, 739:15, 739:24, 740:4, 740:9, 740:13, 741:4, 741:8, 741:10, 741:18, 741:25, 743:3, 743:25, 744:5, 744:16, 744:21, 744:24, 745:2, 746:7, 746:19, 747:13, 747:16, 747:22, 748:2, 748:5, 748:24, 749:25, 751:12, 751:20, 752:13, 752:16, 752:21, 753:1, 753:5, 753:7, 753:22, 754:4, 754:9, 754:21, 755:1, 755:6, 756:4, 756:20, 757:4, 757:20, 758:10, 761:20, 761:25, 762:8, 762:11, 763:15, 763:19, 763:24, 764:3, 765:11, 765:18, 765:21, 766:1, 766:13, 766:19, 766:23, 767:17, 768:3, 768:6, 769:14, 769:17, 769:21, 769:25, 770:11, 770:14, 772:6, 772:18,</p>
--	---	--	---	---

773:18, 773:22, 774:4, 774:7, 774:11, 775:11, 776:19, 777:1, 777:6, 777:9, 777:12, 777:18, 778:1, 778:3, 782:4, 782:22, 783:1, 783:4, 783:6, 783:10, 783:14, 783:19, 783:25, 784:2, 784:7, 784:9, 784:13, 784:15, 785:23, 786:2, 786:10, 786:18, 786:23, 787:5, 787:8, 787:14, 787:15, 787:21, 788:17, 790:15, 790:16, 791:6, 791:7, 791:13, 791:15, 791:24, 792:1, 792:7, 792:9, 792:24, 793:7, 795:6, 795:9, 795:23, 796:1, 796:8, 796:22, 796:23, 798:9, 798:10, 798:18, 798:23, 826:2, 826:6, 826:20, 826:24, 828:5, 828:15, 828:22, 830:6, 850:6, 881:14, 882:11, 882:19, 883:23, 884:1, 884:12, 884:16, 884:23, 885:2, 886:7, 901:19, 909:8 Milliken [11] - 738:3, 750:22, 761:9, 763:7, 763:10, 765:9, 768:22, 775:1, 776:18, 776:25, 777:16 milliken [1] - 733:5 million [1] - 997:6 millions [1] - 997:7 mind [6] - 732:21, 736:15, 748:20, 757:18, 775:11, 797:19 mindset [1] - 809:23 minimize [1] - 807:9 minimum [3] - 849:14, 918:5, 933:21 minus [1] - 805:1 minute [3] - 760:18, 838:18, 895:5	minutes [16] - 708:4, 708:8, 709:8, 709:12, 752:17, 776:20, 776:22, 808:2, 808:13, 813:5, 823:14, 823:16, 824:1, 898:9, 981:19, 984:11 misaligned [1] - 707:16 mischaracterization [1] - 699:12 mismatch [1] - 706:19 missed [1] - 943:24 missing [3] - 675:2, 685:23, 881:22 misspoke [2] - 779:15, 787:22 mistake [2] - 686:6, 988:23 mistakes [1] - 989:2 misunderstanding [2] - 771:8, 944:12 mixed [1] - 906:17 mixing [1] - 827:13 mixture [1] - 769:3 model [1] - 885:15 modest [1] - 842:12 molecule [7] - 689:25, 832:5, 832:15, 840:11, 846:20, 971:4, 971:10 molecules [8] - 832:8, 834:4, 861:10, 862:2, 863:23, 864:5, 873:19, 971:23 moment [7] - 746:8, 758:9, 776:19, 816:4, 836:1, 895:4, 921:15 momentary [1] - 891:22 Monday [3] - 817:14, 891:14, 892:2 money [3] - 811:11, 811:12, 811:16 month [5] - 673:9, 744:6, 759:3, 789:1, 797:6 months [12] - 738:12, 741:1, 753:25, 754:3, 754:6, 754:11, 763:17, 795:12, 846:16, 847:5, 847:10, 997:4 mood [1] - 862:15 morning [16] - 672:5, 672:7, 690:10,	697:13, 700:11, 700:25, 793:14, 793:15, 799:4, 836:15, 869:23, 936:22, 938:6, 938:11, 939:5, 1003:8 morphine [1] - 834:12 MORRIS [1] - 671:12 most [13] - 692:4, 706:14, 706:25, 763:16, 810:2, 869:19, 869:25, 873:12, 885:18, 927:9, 927:20, 930:9, 992:2 mostly [4] - 802:9, 802:11, 892:20, 892:25 motivated [4] - 753:14, 809:24, 813:15, 993:4 motivation [7] - 801:13, 810:18, 814:3, 953:15, 953:21, 978:7, 979:22 mouth [1] - 797:6 move [52] - 709:10, 709:13, 712:9, 713:8, 713:24, 714:10, 714:23, 715:10, 716:2, 717:11, 718:17, 718:24, 719:8, 720:3, 720:14, 721:18, 723:23, 725:5, 725:15, 726:12, 726:24, 728:7, 729:19, 730:5, 730:24, 731:12, 756:21, 781:5, 796:24, 798:18, 804:8, 805:18, 811:18, 815:9, 816:4, 818:21, 820:12, 828:16, 847:17, 849:12, 852:6, 876:3, 876:4, 880:7, 880:15, 904:6, 958:15, 959:4, 961:12, 977:11, 998:12, 999:1 movements [1] - 891:19 moving [5] - 709:8, 816:22, 830:20, 866:3, 984:4 MR [554] - 672:7,	672:18, 673:3, 673:7, 673:11, 673:24, 674:5, 674:6, 674:24, 675:4, 675:7, 675:11, 675:16, 675:20, 676:8, 676:11, 676:18, 676:21, 677:1, 677:4, 677:8, 677:16, 677:20, 677:24, 678:11, 678:15, 679:1, 679:3, 679:22, 680:18, 680:21, 681:3, 681:6, 681:13, 681:15, 681:25, 682:15, 682:17, 682:20, 683:2, 684:8, 684:16, 684:21, 685:9, 685:14, 685:17, 686:20, 687:3, 687:14, 687:16, 689:10, 689:11, 689:17, 689:20, 689:22, 690:1, 690:4, 690:13, 690:15, 690:18, 691:3, 691:8, 692:11, 692:16, 692:20, 693:24, 694:5, 694:10, 694:13, 694:19, 695:1, 695:3, 695:5, 695:6, 695:11, 695:15, 695:22, 696:4, 696:7, 696:9, 696:11, 696:15, 696:18, 697:2, 697:7, 697:16, 697:22, 698:2, 698:9, 698:18, 698:22, 698:23, 699:1, 699:12, 699:20, 699:25, 700:1, 700:5, 700:8, 700:11, 700:24, 711:8, 711:15, 711:17, 711:21, 712:5, 712:11, 713:8, 713:10, 713:13, 714:10, 714:12, 714:15, 715:10, 715:12, 715:15, 717:11, 717:13, 717:19, 718:23, 719:8, 719:10, 719:13, 720:14, 720:16,	720:19, 721:18, 721:20, 721:23, 723:23, 723:25, 724:3, 725:15, 725:17, 725:20, 726:24, 727:1, 727:4, 730:5, 730:7, 730:10, 731:12, 731:14, 731:17, 732:4, 732:6, 732:12, 732:20, 732:25, 733:6, 733:13, 733:16, 733:18, 733:23, 734:6, 734:10, 734:17, 734:21, 735:4, 735:12, 735:21, 736:2, 736:6, 736:10, 736:13, 737:5, 738:15, 739:10, 739:15, 739:24, 740:4, 740:9, 740:13, 741:4, 741:8, 741:10, 741:18, 741:25, 742:3, 742:22, 743:3, 743:14, 743:23, 743:25, 744:5, 744:16, 744:21, 744:24, 745:2, 745:7, 745:17, 745:25, 746:7, 746:10, 746:13, 746:19, 747:13, 747:16, 747:22, 748:2, 748:5, 748:24, 749:25, 750:19, 751:12, 751:20, 752:13, 752:16, 752:21, 753:1, 753:5, 753:7, 753:22, 754:4, 754:9, 754:21, 755:1, 755:6, 756:4, 756:20, 757:4, 757:20, 758:7, 758:10, 758:15, 758:18, 759:3, 759:10, 759:14, 760:5, 760:14, 761:20, 761:25, 762:7, 762:8, 762:11, 763:6, 763:9, 763:15, 763:19, 763:24, 764:3, 764:5, 764:21, 765:11, 765:18, 765:21, 766:1, 766:13,
---	---	--	---	---

766:19, 766:23, 767:17, 768:3, 768:6, 768:18, 768:21, 769:7, 769:14, 769:17, 769:21, 769:25, 770:11, 770:14, 772:6, 772:18, 773:18, 773:22, 774:2, 774:4, 774:7, 774:11, 774:13, 774:20, 775:11, 775:21, 775:25, 776:7, 776:14, 776:19, 777:1, 777:6, 777:9, 777:12, 777:15, 777:18, 778:1, 778:3, 781:12, 781:18, 781:25, 782:4, 782:12, 782:22, 783:1, 783:4, 783:6, 783:10, 783:14, 783:19, 783:25, 784:2, 784:7, 784:9, 784:13, 784:15, 784:18, 784:23, 785:7, 785:23, 786:2, 786:10, 786:18, 786:23, 787:5, 787:8, 787:14, 787:15, 787:20, 787:21, 787:23, 788:2, 788:6, 788:17, 788:19, 790:15, 790:16, 791:6, 791:7, 791:13, 791:15, 791:24, 792:1, 792:7, 792:9, 792:21, 792:24, 793:7, 793:9, 793:13, 794:19, 794:25, 795:6, 795:9, 795:23, 796:1, 796:8, 796:22, 796:23, 798:9, 798:10, 798:18, 798:20, 798:23, 826:2, 826:6, 826:20, 826:24, 828:5, 828:8, 828:15, 828:19, 828:22, 828:25, 830:4, 830:6, 830:9, 830:11, 835:9, 835:12, 835:20, 835:22, 836:22, 836:24, 838:10,	838:13, 840:18, 840:21, 844:23, 845:6, 846:3, 846:5, 847:15, 847:16, 847:20, 847:22, 850:4, 850:6, 850:10, 850:14, 851:19, 851:23, 852:13, 852:15, 853:7, 853:9, 855:9, 855:11, 856:12, 856:14, 860:1, 860:3, 860:17, 860:20, 861:7, 861:9, 863:6, 863:8, 863:17, 863:21, 864:24, 865:1, 866:12, 866:13, 870:21, 870:25, 872:2, 872:7, 872:14, 872:17, 873:4, 873:6, 876:21, 876:25, 880:11, 880:14, 881:14, 881:20, 881:25, 882:9, 882:11, 882:19, 883:23, 884:1, 884:12, 884:16, 884:23, 885:2, 886:7, 894:2, 894:14, 894:22, 894:24, 895:3, 895:14, 895:18, 895:24, 898:18, 898:21, 898:23, 901:5, 901:6, 901:9, 901:10, 901:19, 902:13, 902:14, 902:17, 902:19, 903:17, 903:18, 904:3, 904:7, 905:19, 905:22, 906:6, 906:7, 907:9, 907:11, 908:1, 908:3, 909:8, 911:4, 911:5, 911:8, 911:9, 919:6, 919:7, 919:10, 924:16, 924:19, 924:23, 925:13, 925:15, 934:10, 934:14, 934:17, 935:23, 935:25, 936:2, 937:22, 937:25, 938:5, 938:11, 938:19, 939:4, 939:12, 939:19, 940:2, 940:9, 940:14, 940:17, 941:4, 941:12,	942:22, 943:2, 943:21, 944:1, 944:5, 944:10, 945:8, 945:12, 946:15, 947:23, 948:6, 948:12, 948:16, 948:25, 949:3, 949:17, 951:6, 951:9, 952:5, 952:18, 956:19, 957:2, 958:3, 958:14, 960:21, 960:24, 961:12, 964:13, 965:20, 972:14, 974:2, 975:13, 980:23, 984:2, 984:11, 984:14, 998:11, 998:14, 998:17, 998:19, 998:21, 999:3, 999:8, 999:11, 999:13, 1001:25, 1002:19, 1002:21, 1003:1, 1003:4, 1003:13 MS [56] - 940:25, 941:8, 941:19, 941:24, 942:3, 942:6, 942:10, 942:14, 942:17, 942:24, 943:20, 945:1, 945:4, 946:7, 946:12, 946:20, 947:5, 947:11, 947:16, 948:2, 948:19, 948:22, 949:6, 949:12, 949:14, 950:1, 951:12, 952:6, 952:25, 957:3, 958:8, 959:1, 959:5, 959:6, 961:2, 961:6, 961:14, 964:17, 964:21, 965:3, 965:23, 968:16, 968:19, 972:18, 973:25, 974:5, 975:11, 975:16, 980:21, 981:1, 981:19, 981:21, 983:25, 984:3, 984:5, 984:7 MT [10] - 710:3, 858:3, 858:9, 858:10, 859:4, 859:5, 859:7, 859:8 MT-1 [2] - 799:19, 932:9 MT-2 [2] - 799:20, 932:9	MT1 [1] - 857:17 MT2 [1] - 857:17 multiple [6] - 693:22, 808:1, 888:12, 901:17, 972:3, 997:7 muscle [1] - 891:19 music [1] - 769:12 must [3] - 878:19, 878:25, 879:3 Myers [1] - 674:10	N name [7] - 701:2, 708:14, 888:10, 896:2, 896:17, 903:23, 942:1 named [3] - 770:2, 829:15, 950:16 namely [2] - 761:7, 810:12 names [1] - 903:22 napping [1] - 931:16 narrow [1] - 723:11 narrowed [1] - 750:23 NASA [1] - 898:3 NATHAN [1] - 671:3 Nathaniel [2] - 762:21, 765:17 nature [6] - 756:25, 757:5, 759:7, 761:15, 891:23 NCT [6] - 778:24, 779:18, 785:12, 789:16, 789:17, 793:3 NDA [1] - 969:1 near [2] - 786:14, 887:3 necessarily [12] - 773:8, 790:7, 817:20, 818:3, 833:18, 840:12, 854:2, 868:19, 883:21, 905:7, 1000:4 necessary [6] - 682:7, 735:23, 771:3, 806:1, 842:23, 851:11 need [47] - 672:25, 673:1, 678:22, 679:10, 679:12, 683:18, 683:19, 685:7, 696:21, 729:16, 737:20, 738:9, 754:7, 770:18, 775:3, 775:9, 776:3, 776:18, 800:25,	827:19, 844:18, 853:20, 885:17, 885:18, 905:12, 905:17, 914:16, 923:2, 923:4, 938:8, 940:7, 940:11, 940:14, 956:25, 958:24, 959:4, 977:17, 991:19, 994:22, 995:3, 995:4, 995:17, 996:15, 996:24, 1001:22, 1002:17, 1002:22 needed [3] - 754:12, 918:4, 991:7 needle [1] - 999:20 needle-like [1] - 999:20 needs [2] - 772:3, 806:8 negate [1] - 883:14 negative [2] - 683:16, 843:16 neglected [1] - 828:16 net [1] - 843:11 never [21] - 678:2, 679:4, 680:2, 680:12, 682:5, 686:13, 729:16, 733:14, 734:18, 757:8, 769:7, 769:9, 837:23, 843:2, 863:13, 888:19, 909:7, 923:21, 925:3, 925:9, 965:1 new [2] - 681:12, 786:19 New [7] - 715:6, 715:24, 840:3, 885:15, 888:12, 891:18, 927:24 next [57] - 700:12, 713:24, 714:23, 714:25, 718:24, 720:3, 725:5, 726:12, 728:7, 729:19, 730:25, 744:7, 744:8, 746:15, 767:24, 768:3, 799:22, 816:6, 818:21, 820:12, 829:6, 849:17, 854:8, 856:11, 859:18, 863:3, 874:18, 877:17, 880:7, 880:15, 894:13, 894:15, 903:13, 907:9, 908:1,
---	---	---	---	--	--

909:17, 911:8,
912:23, 913:17,
920:23, 929:9,
930:25, 937:25,
952:13, 955:14,
959:11, 965:8,
966:14, 974:15,
975:1, 976:2, 986:5,
988:8, 988:15,
988:24, 989:19,
994:25
nice [2] - 885:14,
955:20
NICHOLAS [1] - 671:8
NICHOLS [1] - 671:12
night [8] - 741:25,
855:14, 855:18,
855:21, 868:7,
868:9, 868:17, 869:5
nighttime [6] - 789:3,
789:7, 830:23,
832:17, 868:13,
869:17
nine [1] - 927:4
nitrogens [2] - 971:14,
971:15
NMR [3] - 971:20,
971:23, 990:13
NO [1] - 1:6
nobody [4] - 688:2,
774:17, 774:19,
774:20
nominally [1] - 985:20
non [2] - 801:7,
858:11
Non-24 [97] - 700:19,
702:13, 702:19,
703:1, 703:8,
703:10, 703:12,
704:25, 705:2,
705:7, 707:1,
707:20, 707:21,
707:22, 708:13,
709:7, 710:19,
710:25, 712:1,
713:23, 714:20,
715:22, 717:23,
718:16, 719:20,
719:22, 719:25,
720:23, 720:24,
721:1, 721:4,
722:22, 723:1,
723:6, 729:14,
729:16, 729:18,
731:11, 773:3,
773:6, 773:11,
783:12, 783:14,
788:25, 789:7,
789:8, 797:12,
799:11, 799:24,

804:12, 805:13,
806:19, 810:6,
810:17, 811:7,
812:9, 813:21,
816:6, 816:11,
818:9, 819:9, 821:2,
822:25, 824:22,
825:10, 825:15,
825:25, 827:20,
827:24, 830:14,
832:3, 832:19,
832:20, 833:3,
838:15, 841:23,
843:25, 845:10,
845:20, 847:8,
854:19, 854:20,
854:23, 855:1,
862:20, 872:23,
872:25, 879:21,
885:18, 885:24,
904:19, 906:15,
908:11, 919:19,
925:3, 931:11
Non-24-Hour [6] -
778:19, 783:16,
789:20, 803:20,
829:9, 914:16
non-obviousness [1]
- 801:7
non-REM [1] - 858:11
none [8] - 781:19,
784:25, 785:16,
788:14, 935:9,
937:6, 1001:2,
1002:19
nonentrained [4] -
908:21, 908:22,
908:25, 909:2
nonetheless [1] -
839:1
noninfringement [1] -
711:14
nonobvious [1] -
980:5
nonprofit [2] - 735:12,
735:13
nonpublic [1] - 692:14
nonresponsive [1] -
958:15
normal [1] - 676:19
normally [1] - 674:25
notable [1] - 888:10
NOTE [1] - 672:3
note [10] - 771:22,
774:14, 846:8,
893:19, 965:2,
966:5, 967:11,
968:7, 992:6, 992:7
notebook [1] - 941:6
noted [10] - 893:23,

951:11, 969:6,
974:19, 975:23,
976:4, 977:16,
982:5, 983:15, 989:3
notes [3] - 752:21,
799:9, 1003:25
nothing [17] - 681:12,
682:20, 686:18,
699:16, 761:4,
781:14, 781:21,
794:19, 797:25,
880:3, 883:20,
886:8, 935:23,
949:17, 952:17,
952:20, 990:25
notice [11] - 733:8,
734:23, 743:15,
752:22, 753:9,
755:2, 755:11,
755:13, 770:23,
795:25, 796:16
notices [1] - 753:14
noting [1] - 964:24
notion [1] - 825:14
nowhere [1] - 939:21
nuclear [1] - 990:4
Number [1] - 827:1
number [16] - 778:25,
780:19, 783:20,
793:4, 827:3,
849:25, 857:9,
870:14, 888:3,
941:5, 966:25,
967:6, 967:20,
969:8, 969:15,
971:13
numbered [1] - 876:22
numbers [3] - 779:19,
919:21, 994:5
numerous [1] - 810:16

O

O'CONNOR [1] -
671:15
oath [3] - 700:22,
777:23, 949:24
Oberlin [1] - 701:22
object [13] - 673:19,
733:14, 742:12,
750:25, 751:18,
756:22, 777:15,
781:12, 785:1,
794:21, 794:25,
881:14, 956:25
objected [4] - 750:5,
756:12, 893:22,
938:14
objecting [5] - 691:3,
732:14, 750:1,

938:9, 958:17
objection [89] -
673:12, 690:14,
713:10, 714:12,
715:12, 717:13,
719:10, 720:16,
721:20, 723:25,
725:17, 727:1,
730:7, 731:15,
731:21, 732:8,
732:9, 737:8,
737:10, 737:12,
737:16, 742:4,
748:7, 749:14,
749:15, 749:24,
750:4, 750:14,
750:16, 750:21,
751:5, 751:14,
756:16, 756:25,
760:22, 761:2,
768:17, 771:15,
771:20, 771:21,
772:1, 772:8,
776:14, 777:3,
777:13, 781:23,
782:12, 782:21,
784:18, 786:7,
787:24, 788:1,
788:2, 792:21,
798:20, 828:18,
830:6, 850:6,
881:24, 893:20,
894:6, 898:21,
901:6, 902:14,
911:5, 919:7,
934:15, 945:6,
948:17, 951:6,
951:8, 951:9,
952:16, 952:18,
956:19, 958:14,
960:21, 961:9,
961:11, 964:13,
965:20, 972:14,
974:2, 975:13,
980:23, 984:2,
999:2, 999:4, 999:6
objections [3] -
761:12, 893:25,
958:3
objectively [1] -
891:19
obligated [1] - 687:7
observe [1] - 693:25
observed [1] - 892:1
obtain [1] - 999:20
obtained [1] - 947:24
obvious [26] - 688:20,
689:1, 800:15,
800:16, 801:1,
801:10, 818:24,

819:1, 819:12,
819:16, 819:23,
820:1, 820:2, 820:7,
820:16, 820:18,
821:16, 821:20,
822:11, 823:9,
855:25, 935:21,
953:2, 953:4, 979:16
obviously [5] - 676:8,
676:10, 718:2,
735:1, 781:15
obviousness [21] -
673:17, 704:10,
712:8, 772:21,
800:23, 801:7,
801:25, 815:8,
822:4, 822:8,
822:10, 854:16,
872:9, 876:8,
877:23, 938:21,
972:19, 972:22,
978:12, 979:11,
998:22
occasioned [1] -
695:20
occurred [2] - 738:12,
933:4
occurring [1] - 830:15
occurs [2] - 898:17,
932:8
ocean [2] - 890:15,
890:16
October [2] - 739:4,
754:19
odd [1] - 680:14
OF [1] - 1:3
off-the-wall [1] - 898:2
offer [18] - 673:22,
699:10, 732:13,
793:7, 830:4, 850:5,
898:19, 901:5,
902:13, 907:6,
911:2, 911:4, 919:6,
958:2, 965:19,
973:25, 975:11,
980:21
offered [7] - 696:19,
705:16, 731:18,
731:19, 802:13,
934:12, 948:16
offering [7] - 703:3,
732:3, 760:15,
760:25, 789:22,
898:25, 899:4
Office [9] - 972:25,
973:6, 973:12,
973:21, 974:10,
974:18, 974:24,
975:7, 976:8
office [3] - 686:3,

<p>686:24, 697:13 often [6] - 672:16, 710:3, 735:14, 893:2, 992:3, 992:4 OHSU [1] - 701:17 older [1] - 849:23 omission [1] - 688:13 once [4] - 821:10, 821:13, 844:18, 874:7 one [174] - 673:11, 681:2, 682:10, 686:15, 686:23, 690:25, 693:19, 696:11, 698:9, 700:9, 710:5, 713:20, 717:25, 718:8, 731:14, 735:15, 737:5, 743:3, 744:6, 745:19, 746:2, 746:15, 751:14, 758:8, 759:14, 767:23, 769:14, 770:2, 772:22, 776:2, 776:19, 777:9, 781:16, 785:15, 787:11, 789:2, 794:1, 796:11, 799:24, 801:10, 816:6, 818:21, 828:2, 828:15, 829:12, 829:19, 833:18, 834:3, 834:14, 834:15, 834:16, 837:20, 839:11, 839:14, 839:19, 840:13, 841:6, 841:7, 841:14, 842:13, 843:25, 846:21, 847:17, 847:18, 848:3, 848:23, 851:21, 852:10, 853:1, 853:22, 854:15, 855:12, 857:1, 858:21, 859:18, 859:22, 861:21, 861:23, 864:16, 864:20, 865:12, 865:16, 870:16, 871:14, 871:16, 871:24, 872:4, 872:8, 874:3, 876:7, 877:22, 879:24, 879:25, 882:5, 882:14, 890:8, 890:18, 893:17, 894:4, 896:25,</p>	<p>897:4, 897:11, 897:12, 897:20, 897:22, 898:13, 905:4, 905:14, 905:23, 906:3, 906:20, 907:4, 907:19, 909:9, 910:1, 912:2, 912:19, 912:25, 913:5, 914:17, 914:19, 915:22, 916:8, 916:21, 919:4, 919:11, 919:23, 920:1, 920:6, 922:18, 922:23, 924:6, 927:3, 939:9, 943:7, 943:16, 943:21, 943:23, 944:10, 944:15, 944:16, 948:15, 955:22, 957:22, 960:10, 962:9, 965:4, 965:16, 974:22, 980:18, 987:8, 988:4, 989:20, 991:17, 992:7, 994:16, 995:20, 997:11, 997:12, 997:24, 998:19, 998:20, 998:21, 998:22, 998:23, 1001:8, 1001:11, 1002:10, 1003:15 one-third [1] - 893:17 one-to-one [1] - 833:18 one-year [1] - 776:2 onerous [3] - 849:14, 977:17, 996:18 ones [4] - 817:24, 832:23, 875:18, 982:4 ongoing [6] - 799:9, 809:4, 811:6, 878:3, 879:20, 880:4 online [4] - 753:23, 754:6, 754:11, 893:21 onset [7] - 702:20, 850:24, 867:7, 868:2, 868:5, 869:13, 875:3 open [6] - 734:24, 743:11, 752:18, 785:3, 829:4, 938:5 open-to-the-public [1] - 752:18 opened [1] - 786:19 opening [2] - 688:22,</p>	<p>773:23 operate [1] - 887:11 operates [1] - 742:7 operative [1] - 744:14 opiate [1] - 834:14 opiates [2] - 834:9, 834:10 opine [2] - 750:12, 946:5 opined [2] - 679:1, 759:14 Opinion [1] - 875:2 opinion [35] - 673:22, 678:5, 678:9, 678:11, 679:5, 682:4, 694:21, 710:16, 715:8, 733:15, 742:8, 789:23, 790:7, 802:5, 809:17, 817:16, 823:8, 824:20, 833:9, 845:9, 879:9, 879:14, 881:17, 881:21, 950:15, 950:22, 950:23, 953:1, 954:11, 960:22, 964:14, 968:4, 972:6, 972:12, 979:15 opinions [52] - 701:9, 701:10, 703:4, 703:18, 703:22, 703:24, 704:1, 704:6, 704:9, 704:10, 704:14, 705:9, 713:6, 714:8, 717:9, 719:6, 720:12, 721:16, 723:21, 724:19, 725:13, 726:22, 728:16, 730:3, 794:14, 797:1, 798:16, 800:12, 801:25, 818:23, 822:9, 825:17, 855:24, 886:5, 898:25, 899:1, 899:3, 923:23, 926:19, 953:7, 953:10, 953:23, 953:25, 956:3, 957:25, 965:17, 972:20, 973:23, 975:9, 977:24, 979:10, 980:19 opportunity [3] - 711:2, 711:16, 803:3 opposed [2] - 681:2, 832:14</p>	<p>opposite [4] - 675:1, 836:3, 836:16, 889:18 opposition [1] - 707:13 optimal [2] - 718:1, 723:7 optimization [1] - 717:24 optimizing [1] - 718:9 option [2] - 709:2, 709:4 or.. [1] - 832:8 oral [3] - 673:1, 882:22, 929:13 orally [2] - 806:12, 830:20 orange [1] - 823:15 order [12] - 682:7, 685:3, 711:8, 711:9, 711:17, 734:24, 758:21, 759:2, 759:22, 775:22, 845:10, 846:19 ordinary [23] - 705:11, 705:17, 753:12, 801:4, 802:20, 811:13, 813:14, 879:5, 883:6, 885:25, 891:1, 891:6, 893:9, 953:24, 954:4, 954:8, 954:12, 954:15, 954:21, 955:11, 955:25, 977:22, 990:9 Oregon [5] - 701:16, 701:24, 702:5, 702:16, 886:20 organic [2] - 954:6, 955:1 organizations [1] - 702:2 orient [1] - 712:13 origin [1] - 692:24 original [3] - 967:15, 967:20, 969:22 originally [2] - 756:6, 761:18 otherwise [2] - 792:12, 811:15 outcome [3] - 789:3, 789:9, 793:5 outline [1] - 689:2 outside [3] - 858:13, 881:14, 990:16 overall [5] - 684:4, 718:11, 718:14, 843:17, 966:3 overrule [2] - 786:7,</p>	<p>881:24 overruled [3] - 782:21, 958:19, 972:16 oversimplified [1] - 867:10 overview [2] - 701:7, 701:8 own [5] - 704:10, 705:21, 765:4, 868:4, 956:4 oxygen [2] - 971:14, 971:15</p>
				P
				<p>P-value [1] - 877:13 p.m [13] - 901:14, 902:23, 904:20, 906:17, 913:1, 913:10, 913:15, 914:22, 916:5, 916:10, 920:1, 923:16, 1003:23 P1 [3] - 988:6, 988:8, 989:1 P2 [1] - 989:22 P3 [2] - 970:24, 989:22 P4 [1] - 989:22 P450 [1] - 704:17 P5 [16] - 968:11, 969:5, 969:6, 969:17, 969:19, 972:5, 988:15, 988:19, 989:3, 989:5, 989:22, 990:22, 990:24, 991:1, 991:4 pacemaker [3] - 706:8, 707:25, 713:21 pacemaker's [1] - 804:2 Pack [1] - 891:5 Page [51] - 754:16, 754:17, 805:3, 806:3, 809:14, 813:7, 826:21, 830:9, 835:10, 835:20, 838:10, 843:20, 845:16, 847:19, 851:18, 853:5, 855:8, 861:7, 863:3, 863:18, 873:1, 876:23, 881:6, 884:13, 884:25, 926:2, 927:13, 928:25, 930:5, 931:19, 931:24, 941:19, 942:14, 959:11,</p>

959:21, 961:15,
961:25, 963:1,
963:11, 964:5,
965:25, 967:1,
967:7, 969:14,
974:7, 975:17,
984:22, 990:20,
994:3

page [48] - 731:7,
731:8, 738:25,
739:2, 739:3,
744:10, 744:23,
746:5, 746:15,
749:13, 752:12,
752:13, 757:7,
757:14, 762:12,
763:11, 778:20,
778:22, 779:13,
780:10, 780:20,
786:22, 793:20,
804:19, 812:21,
850:15, 856:11,
863:3, 863:20,
865:2, 866:8,
866:11, 874:18,
876:20, 882:13,
882:14, 925:20,
937:3, 944:23,
959:11, 967:9,
973:4, 974:15,
986:4, 986:5,
989:17, 999:16

Pages [3] - 794:13,
795:15, 806:10

pages [7] - 738:22,
739:1, 756:15,
815:6, 826:12,
826:13, 969:12

pancreatitis [1] -
900:18

Pandi [2] - 820:17,
820:19

Pandi-Perumal [2] -
820:17, 820:19

paper [103] - 713:3,
713:5, 713:15,
714:5, 714:7,
714:16, 715:5,
715:7, 715:16,
715:19, 715:20,
716:11, 716:19,
716:25, 717:6,
718:8, 719:5,
720:11, 725:11,
725:12, 725:21,
726:1, 728:13,
746:2, 746:13,
746:20, 829:3,
839:14, 839:19,
840:3, 840:6,

842:13, 851:14,
852:16, 854:13,
855:5, 856:18,
857:6, 859:19,
863:4, 864:13,
864:15, 864:22,
866:6, 866:7,
866:15, 866:16,
870:4, 872:8,
872:24, 877:19,
878:1, 883:12,
884:10, 900:7,
900:12, 901:2,
901:12, 901:23,
902:11, 902:20,
904:13, 906:8,
906:14, 907:7,
907:13, 908:5,
909:10, 910:22,
911:11, 917:14,
918:3, 919:13,
919:14, 919:23,
920:9, 925:16,
925:21, 926:5,
926:15, 926:18,
927:15, 927:17,
927:23, 928:7,
928:10, 929:17,
929:21, 929:25,
930:17, 930:22,
932:21, 932:23,
933:12, 933:13,
937:8, 946:14,
946:17, 957:23,
964:18, 964:19

papers [10] - 717:8,
717:21, 718:12,
840:1, 852:10,
897:11, 909:19,
919:17, 919:22,
929:6

paragraph [38] -
736:4, 739:9, 753:7,
759:24, 762:22,
838:11, 840:19,
843:21, 847:21,
851:20, 851:21,
863:6, 866:10,
876:22, 876:24,
884:3, 929:1, 929:2,
932:1, 933:16,
935:8, 936:24,
941:23, 941:24,
952:3, 952:13,
959:17, 963:3,
964:6, 969:4, 974:8,
975:18, 976:1,
976:2, 981:11,
989:20, 999:18

Paragraph [16] -
736:6, 742:5,

758:21, 785:8,
786:3, 788:16,
788:20, 788:22,
941:20, 942:15,
942:22, 943:10,
946:4, 946:5, 952:10
paragraphs [5] -
860:19, 939:7,
946:6, 961:5, 974:17
paralegal [2] - 741:14,
741:15

paralegals [1] - 737:1

parameters [3] -

703:12, 723:3,
723:18

pardon [2] - 1000:9,
1001:19

parent [1] - 982:15

part [36] - 673:17,
675:11, 676:24,
684:25, 687:8,
693:23, 700:20,
703:15, 711:10,
739:21, 746:23,
760:24, 766:15,
766:22, 784:4,
784:10, 841:3,
843:3, 843:15,
847:11, 863:20,
870:23, 887:16,
905:5, 913:18,
914:6, 926:2, 926:4,
926:18, 929:1,
938:2, 966:3,
966:13, 966:21,
972:10, 999:17

partially [1] - 887:6

particular [23] - 704:5,

704:16, 727:24,
731:24, 734:16,
735:8, 744:2,
744:10, 754:18,
821:25, 833:14,
840:11, 846:20,
851:10, 853:23,
865:3, 870:22,
927:23, 931:4,
960:10, 969:11,
969:12, 987:22

particularly [2] -
797:17, 841:22

parties [10] - 672:10,
682:7, 700:14,
770:22, 771:6,
774:15, 800:4,
897:5, 944:18,
946:13

partly [2] - 831:18,
846:24

party [2] - 682:1,

887:12
pass [4] - 828:5,
924:17, 924:19,
941:1

passages [1] - 815:4

patent [170] - 673:4,
673:18, 673:23,
674:1, 675:22,
675:24, 676:6,
676:13, 676:21,
679:3, 680:11,
680:17, 684:13,
684:15, 684:17,
684:21, 684:22,
684:24, 685:2,
685:5, 685:19,
686:2, 686:3,
686:23, 686:24,
687:18, 687:19,
688:16, 688:17,
688:20, 691:14,
704:22, 705:1,
705:5, 724:18,
724:21, 724:23,
724:25, 726:18,
726:19, 726:20,
727:5, 735:14,
741:1, 762:4,
764:19, 772:21,
773:24, 773:25,
774:4, 795:13,
800:11, 803:10,
804:9, 809:20,
811:25, 813:12,
814:5, 815:8,
815:25, 816:2,
816:16, 817:10,
817:18, 818:2,
818:3, 818:6,
818:21, 818:23,
819:4, 819:7,
819:17, 819:18,
820:12, 820:21,
820:22, 821:2,
821:3, 821:10,
821:12, 821:21,
821:22, 822:7,
822:8, 822:10,
822:15, 822:18,
822:21, 822:23,
823:4, 824:6,
824:21, 825:4,
825:23, 826:7,
826:10, 826:15,
827:4, 827:5, 827:8,
827:12, 828:17,
876:11, 876:14,
880:24, 881:3,
881:21, 882:2,
882:3, 938:21,
938:23, 939:16,

943:12, 947:21,
948:4, 953:2, 953:3,
953:5, 953:11,
954:3, 954:12,
959:9, 960:6,
960:18, 960:20,
962:15, 972:7,
973:4, 973:7, 973:9,
973:10, 974:13,
974:14, 974:21,
975:21, 975:24,
976:5, 976:9,
976:13, 976:15,
978:3, 978:10,
979:16, 980:5,
982:5, 982:11,
982:12, 982:13,
982:14, 982:15,
991:7, 992:16,
993:7, 997:21,
997:25, 998:6,
998:7, 1000:7,
1000:11, 1000:17,
1001:13, 1002:3,
1002:6

Patent [10] - 826:25,
972:25, 973:6,
973:12, 973:20,
974:10, 974:18,
974:24, 975:6, 976:8

patentable [1] -
688:24

patented [1] - 766:4

patents [16] - 674:18,
686:5, 703:16,
703:19, 704:2,
704:3, 704:11,
704:20, 704:22,
705:10, 761:14,
800:9, 819:12,
821:16, 828:1,
935:21

patents-in-suit [1] -
935:21

path [6] - 696:12,
696:14, 963:10,
963:15, 977:10,
977:16

pathways [1] - 881:9

patient [7] - 773:19,
808:23, 816:6,
823:13, 843:15,
925:3, 925:9

patient's [3] - 813:1,
849:1, 915:12

patients [30] - 703:17,
714:21, 718:8,
773:3, 773:11,
788:25, 789:1,
789:8, 797:7,

797:11, 804:21,
811:7, 817:7,
818:16, 818:19,
827:24, 827:25,
833:3, 846:9,
846:13, 879:25,
880:1, 887:17,
899:8, 902:5,
909:24, 909:25,
910:4, 922:21,
928:15
pattern [1] - 901:15
PAUL [1] - 671:8
pause [2] - 894:15,
921:15
PCR [1] - 835:23
PDX [5] - 899:14,
902:18, 903:17,
909:17, 911:8
PDX-09 [2] - 970:8,
981:23
PDX-09.10 [1] - 970:6
PDX-8.16 [1] - 912:15
PDX-8.18 [1] - 913:25
PDX-8.2 [1] - 899:3
PDX-8.21 [1] - 915:25
PDX-8.28 [1] - 920:17
PDX-8.29 [1] - 923:9
PDX-8.9 [1] - 906:6
PDX-9 [1] - 950:7
peak [3] - 688:9,
847:23, 987:9
peer [1] - 928:2
peer-reviewed [1] -
928:2
pending [2] - 782:20,
786:5
People [1] - 850:17
people [55] - 676:15,
681:23, 683:6,
693:3, 693:4, 693:7,
694:21, 699:11,
704:8, 707:15,
708:23, 710:25,
723:5, 736:21,
742:15, 798:3,
799:11, 809:5,
829:20, 836:19,
838:2, 838:7,
840:24, 846:17,
846:21, 854:19,
854:20, 858:16,
867:18, 874:3,
891:13, 896:22,
897:1, 897:14,
902:12, 905:2,
906:25, 908:23,
914:16, 918:9,
919:19, 924:4,
927:9, 929:12,

930:9, 930:14,
932:15, 934:2,
935:10, 937:7,
940:18, 955:8,
991:21, 992:13,
993:7
per [8] - 855:18,
855:21, 873:13,
873:23, 875:4,
875:9, 921:14, 995:2
percent [36] - 830:16,
846:9, 846:13,
846:16, 867:2,
870:8, 877:2, 893:7,
967:12, 967:13,
968:1, 972:23,
983:7, 993:5,
994:22, 995:2,
995:15, 995:17,
996:1, 996:7, 996:8,
996:14, 997:10,
997:13, 999:21,
999:22, 999:24,
1000:1, 1000:2,
1000:5, 1000:10,
1000:14, 1000:15,
1000:19, 1000:25
perception [2] - 809:5,
821:7
percolating [1] -
672:20
perfect [1] - 757:9
performed [2] -
926:22, 985:13
perhaps [8] - 674:10,
842:12, 845:13,
853:20, 867:9,
992:7, 997:8, 997:22
period [26] - 754:3,
776:2, 789:1, 797:6,
802:3, 802:11,
802:17, 802:22,
802:23, 803:4,
804:22, 838:7,
852:22, 855:24,
880:20, 892:9,
892:22, 893:1,
908:24, 909:2,
909:19, 916:10,
921:13, 921:23,
922:10, 922:18
periodicity [2] - 706:7,
706:9
periods [1] - 922:9
perm [1] - 835:23
permission [1] - 783:1
permit [1] - 790:14
Perni [24] - 674:8,
690:19, 691:12,
696:16, 940:18,

943:11, 944:2,
946:21, 947:3,
948:21, 948:23,
948:25, 949:13,
949:14, 950:13,
952:10, 956:7,
956:10, 973:1,
976:15, 977:16,
978:14, 978:18,
979:6
Perni's [18] - 941:1,
941:21, 948:20,
950:15, 953:1,
954:11, 954:14,
954:18, 954:21,
955:4, 955:12,
955:15, 956:1,
956:4, 957:22,
976:12, 978:12,
979:11
person [58] - 676:14,
699:23, 705:10,
705:17, 705:20,
722:21, 729:4,
736:16, 736:23,
748:13, 749:18,
749:22, 801:3,
802:5, 802:8, 802:9,
802:21, 809:23,
809:24, 810:23,
811:8, 811:13,
813:14, 814:9,
833:10, 840:10,
852:2, 852:21,
853:19, 879:5,
883:5, 885:25,
896:21, 897:9,
901:13, 904:10,
905:9, 905:14,
906:20, 914:24,
921:11, 922:17,
924:6, 950:16,
953:24, 954:3,
954:5, 954:8,
954:11, 954:15,
954:21, 954:25,
955:11, 955:25,
958:22, 977:21,
988:11, 992:11
person's [1] - 915:4
persons [2] - 753:12,
927:20
Perumal [2] - 820:17,
820:19
pharma [1] - 701:15
pharma-psychiatry
[1] - 701:15
Pharmaceutical [1] -
727:6
pharmaceutical [3] -

683:23, 991:7, 993:3
PHARMACEUTICAL
S [2] - 1:5, 1:7
Pharmaceuticals [5] -
671:6, 671:13,
751:24, 980:16
pharmacokinetics [3]
- 726:2, 820:10,
857:6
pharmacologist [1] -
822:6
pharmacology [1] -
704:16
phase [97] - 709:9,
709:15, 713:16,
713:21, 718:15,
718:19, 722:8,
728:21, 729:1,
729:12, 730:17,
743:15, 789:10,
803:25, 804:1,
810:13, 812:5,
813:24, 814:23,
835:1, 835:23,
837:9, 837:14,
837:24, 838:4,
838:8, 841:4,
841:15, 842:5,
842:22, 843:2,
843:5, 843:6,
844:12, 850:17,
850:18, 850:24,
851:3, 851:4, 851:7,
851:8, 851:11,
852:3, 853:25,
854:1, 858:10,
862:23, 864:10,
870:11, 870:17,
871:10, 871:17,
874:22, 875:7,
875:8, 875:16,
876:16, 877:4,
877:5, 883:12,
883:14, 883:17,
883:19, 883:21,
884:19, 885:16,
885:19, 885:22,
899:9, 902:24,
903:2, 904:23,
905:6, 905:10,
906:20, 912:6,
912:22, 913:3,
913:18, 914:6,
914:15, 916:5,
916:24, 920:21,
921:6, 921:9, 922:7,
922:25, 923:1,
924:13, 927:18,
932:7, 932:13, 933:5
Phase [29] - 728:19,

731:10, 736:9,
739:14, 739:16,
770:11, 773:2,
779:9, 783:22,
788:23, 793:5,
796:25, 799:5,
799:6, 799:10,
799:13, 806:18,
811:6, 811:11,
811:16, 815:13,
878:3, 878:18,
878:24, 885:3,
885:12, 961:17
phase-advancing [1] -
927:18
phase-resetting [1] -
803:25
phased [1] - 851:25
PhD [6] - 896:11,
896:12, 896:14,
904:1, 925:2, 955:1
phenomenon [1] -
890:4
phosgene [1] - 951:19
phrase [9] - 802:2,
802:6, 802:13,
802:20, 803:2,
803:3, 831:5, 877:6,
912:9
Phrase [1] - 809:4
physician [1] - 701:18
physicians [1] -
835:18
Physicians [1] - 702:5
physiological [4] -
706:5, 858:7,
925:24, 926:10
physiology [6] -
700:18, 702:9,
702:13, 702:25,
703:10, 887:18
pick [3] - 807:5,
865:12, 887:4
PICKARD [1] - 671:4
piece [5] - 678:17,
681:8, 692:14,
887:9, 944:6
pieced [1] - 991:3
pieces [3] - 879:7,
940:10, 971:3
pineal [1] - 867:21
place [1] - 869:25
placebo [9] - 788:25,
789:2, 804:24,
817:1, 855:17,
870:9, 871:16,
884:20, 927:3
Placebo [2] - 778:18,
789:19
places [3] - 808:3,

<p>970:21, 978:15 plain [1] - 802:20 plainly [2] - 769:3, 785:18 Plaintiff [1] - 1:5 plaintiff [1] - 894:17 plaintiff's [3] - 681:10, 737:11, 756:21 Plaintiff's [2] - 850:5, 850:8 plaintiffs [5] - 681:1, 711:12, 756:12, 777:2, 947:22 plan [3] - 788:24, 1003:9, 1003:10 planes [1] - 866:4 planet [1] - 898:8 planning [2] - 677:25, 848:17 Platt [6] - 677:2, 684:1, 685:7, 685:10, 686:1, 688:8 play [3] - 858:6, 858:10, 897:17 players [1] - 866:3 plays [2] - 772:19, 858:11 plot [1] - 912:20 plotted [2] - 836:19, 912:23 plus [2] - 773:19, 804:25 point [81] - 676:23, 677:24, 678:1, 680:10, 680:19, 681:4, 685:1, 685:4, 689:14, 692:5, 695:7, 696:11, 696:18, 698:13, 712:13, 722:10, 737:15, 744:2, 748:3, 748:8, 751:13, 751:22, 754:4, 754:9, 756:11, 757:20, 760:22, 761:3, 762:1, 762:11, 766:1, 766:6, 767:1, 768:17, 769:15, 770:16, 772:24, 773:12, 809:4, 810:11, 810:16, 831:13, 841:15, 843:2, 844:13, 844:20, 845:9, 845:15, 850:4, 854:4, 856:25, 860:9, 860:21, 863:9, 867:10, 867:17, 867:24,</p>	<p>874:17, 882:17, 899:23, 899:25, 912:24, 917:19, 939:23, 944:11, 944:13, 944:15, 944:16, 947:1, 947:24, 954:24, 960:25, 961:10, 966:5, 977:21, 978:24, 987:12, 997:15, 1001:23 pointed [5] - 695:13, 757:22, 776:9, 812:6, 884:5 pointer [1] - 912:25 pointing [4] - 746:23, 855:23, 884:2, 961:4 points [11] - 710:17, 755:23, 803:24, 806:19, 806:25, 808:1, 809:6, 814:12, 954:20, 978:25 poison [1] - 683:13 polymeropoulos [1] - 891:14 Polymeropoulos [1] - 825:5 population [1] - 922:1 portion [8] - 766:3, 803:1, 809:14, 812:10, 823:24, 842:17, 966:23, 967:4 portions [1] - 805:15 Portland [1] - 701:14 POSA [1] - 879:10 posited [1] - 848:23 positing [1] - 853:10 position [7] - 710:21, 710:22, 773:7, 785:5, 815:11, 817:22, 943:20 positions [1] - 701:12 positive [3] - 740:10, 843:14, 845:13 possession [1] - 824:15 possible [13] - 683:21, 688:14, 807:6, 826:5, 834:19, 834:23, 842:3, 852:3, 852:4, 854:5, 892:20, 987:7, 987:12 possibly [4] - 691:17, 692:6, 932:9, 969:22 post [3] - 672:12, 772:5, 772:11 post-2015 [1] - 758:3</p>	<p>post-trial [2] - 772:5, 772:11 posted [22] - 733:9, 740:25, 742:20, 745:14, 745:15, 745:23, 747:10, 747:13, 752:2, 754:11, 755:16, 761:18, 767:22, 775:5, 775:6, 780:25, 782:9, 782:14, 791:11, 792:20, 794:2, 795:11 posters [7] - 934:22, 935:1, 936:7, 936:11, 936:12, 936:14, 936:19 posting [3] - 759:8, 770:4, 780:6 posttrial [2] - 691:21, 751:7 potential [5] - 799:17, 915:11, 951:18, 968:21, 979:20 potentially [4] - 683:24, 854:1, 914:4, 978:4 PowerPoint [1] - 935:2 practice [5] - 703:12, 723:2, 723:18, 817:18, 850:2 Practice [1] - 918:20 Prasad [1] - 958:12 PRC [6] - 842:18, 853:17, 912:9, 913:19, 914:6, 916:24 PRCs [1] - 836:2 preamble [3] - 816:5, 817:12, 817:24 precedence [1] - 796:2 precise [2] - 857:19, 867:13 precisely [5] - 723:10, 748:2, 798:3, 843:13, 905:13 Preclinical [1] - 959:13 preclinical [2] - 863:10, 959:23 predicate [2] - 737:3, 742:11 predict [2] - 921:10, 921:22 predictions [1] - 922:6 preeminent [1] - 896:20</p>	<p>prefer [1] - 941:12 preferable [2] - 848:24, 907:14 preference [1] - 939:20 preferred [1] - 927:4 prejudicial [3] - 785:2, 785:21, 788:4 preliminaries [1] - 703:25 preliminary [1] - 959:19 premised [1] - 751:14 preparation [1] - 976:7 prepare [8] - 950:4, 950:19, 965:24, 967:17, 970:2, 973:3, 976:24, 977:24 prepared [14] - 701:3, 703:21, 705:13, 707:2, 711:24, 898:24, 899:11, 909:18, 912:12, 913:9, 920:14, 923:5, 923:22, 1003:6 prescribe [1] - 925:6 prescribing [1] - 817:19 presence [4] - 962:23, 983:17, 986:17, 987:7 present [9] - 762:14, 817:13, 841:2, 843:1, 926:7, 930:7, 974:23, 981:14, 985:12 presentation [1] - 912:17 presented [4] - 686:11, 764:15, 936:13, 981:8 presenting [1] - 894:18 presents [1] - 912:19 preserved [1] - 957:1 pressed [2] - 738:1, 741:7 prestigious [1] - 888:2 presumably [6] - 679:13, 681:17, 746:19, 875:11, 875:18, 932:8 presume [1] - 679:23 presumed [1] - 707:16 pretrial [12] - 711:9, 734:23, 743:15, 758:5, 758:20,</p>	<p>759:2, 759:22, 775:17, 775:18, 775:22, 796:16, 894:7 pretty [7] - 688:5, 742:14, 752:5, 774:10, 837:15, 843:16, 960:19 prevalence [1] - 830:14 prevent [1] - 686:5 preview [1] - 712:5 previous [6] - 786:19, 810:21, 907:3, 930:13, 962:6, 989:17 previously [4] - 834:7, 958:4, 974:20, 993:8 primary [2] - 789:2, 880:1 principal [2] - 897:21, 900:7 principle [1] - 773:23 print [2] - 757:5, 763:1 printed [1] - 766:4 printout [3] - 738:20, 755:24, 763:2 priority [17] - 674:15, 675:23, 676:13, 687:18, 691:14, 694:25, 741:1, 762:3, 764:2, 764:6, 764:7, 766:17, 795:12, 910:13, 916:11, 917:10, 919:1 private [3] - 735:10, 735:13, 888:21 probative [2] - 767:8, 797:17 problem [11] - 678:2, 686:15, 686:21, 686:22, 687:7, 692:10, 745:17, 753:3, 769:2, 948:1, 993:9 procedure [2] - 679:20, 692:8 procedures [1] - 985:6 proceed [1] - 778:1 proceeding [2] - 1003:22, 1004:1 proceedings [1] - 800:5 proceeds [1] - 740:7 Process [1] - 961:16 process [59] - 674:11, 675:9, 675:14, 675:24, 676:12, 676:14, 676:25,</p>
---	---	---	---	--

<p>679:8, 680:5, 680:7, 682:11, 683:12, 683:15, 683:19, 684:25, 688:24, 689:25, 690:6, 691:13, 692:5, 692:21, 693:4, 693:6, 694:4, 695:12, 697:17, 697:23, 698:7, 698:11, 698:17, 699:2, 699:4, 699:5, 745:10, 918:12, 938:13, 939:21, 940:3, 940:8, 940:10, 940:12, 940:21, 945:20, 947:25, 951:1, 951:17, 953:13, 953:20, 958:18, 963:9, 965:2, 966:11, 983:9, 983:17, 983:23, 1001:12, 1001:24, 1002:4</p> <p>processes [1] - 964:12</p> <p>produce [6] - 851:15, 851:25, 852:3, 867:11, 869:10, 961:23</p> <p>produced [5] - 680:6, 683:24, 688:7, 760:6, 832:8</p> <p>producing [2] - 842:22, 869:11</p> <p>product [14] - 687:11, 688:4, 693:7, 693:13, 968:23, 970:19, 974:23, 976:23, 987:16, 995:12, 995:15, 995:23, 996:3, 1000:13</p> <p>production [2] - 868:5, 965:1</p> <p>products [1] - 991:7</p> <p>profer [1] - 940:19</p> <p>professional [1] - 702:1</p> <p>Professor [1] - 900:8</p> <p>professor [1] - 701:15</p> <p>proffer [1] - 678:24</p> <p>proffering [2] - 766:11</p> <p>program [1] - 887:8</p> <p>progressive [2] - 708:10, 908:12</p> <p>promote [1] - 937:21</p> <p>promotion [1] - 858:11</p>	<p>prompted [1] - 691:23</p> <p>prone [1] - 990:13</p> <p>proof [4] - 711:9, 711:17, 733:2, 750:9</p> <p>proofs [1] - 764:15</p> <p>propensity [3] - 706:15, 708:6, 708:11</p> <p>proper [5] - 844:2, 844:11, 914:12, 914:15</p> <p>properly [1] - 750:5</p> <p>properties [2] - 848:14, 891:24</p> <p>Properties [1] - 863:7</p> <p>property [1] - 795:19</p> <p>propionyl [3] - 962:22, 963:21, 963:23</p> <p>propionylated [1] - 1001:16</p> <p>propionylating [8] - 951:15, 952:2, 952:4, 956:17, 957:7, 960:1, 962:19, 963:17</p> <p>proponent [2] - 748:12, 763:8</p> <p>proposal [1] - 972:5</p> <p>proposals [1] - 972:3</p> <p>propose [1] - 848:7</p> <p>proposed [6] - 853:12, 912:3, 970:3, 970:12, 972:2, 990:24</p> <p>proposes [1] - 746:1</p> <p>proposing [1] - 689:15</p> <p>proposition [1] - 795:14</p> <p>propylinating [1] - 942:12</p> <p>prosecution [1] - 704:3</p> <p>protocol [42] - 739:16, 739:19, 740:14, 740:16, 740:17, 740:19, 740:21, 740:23, 744:18, 746:21, 747:3, 747:17, 756:9, 756:10, 758:2, 762:2, 766:14, 766:15, 766:25, 767:22, 767:25, 770:9, 770:10, 770:12, 773:1, 773:13, 778:11, 780:15, 782:9, 787:10, 790:18, 790:22, 792:19,</p>	<p>795:11, 795:15, 797:1, 797:3, 815:13, 816:20, 817:4, 817:6</p> <p>protocols [2] - 740:6, 740:7</p> <p>prove [6] - 745:8, 760:20, 761:1, 764:16, 764:25, 769:10</p> <p>proven [5] - 733:1, 760:17, 776:15, 803:25, 932:10</p> <p>proves [1] - 949:21</p> <p>provide [8] - 796:3, 935:20, 937:3, 949:7, 954:20, 978:6, 979:10, 979:22</p> <p>provided [3] - 677:16, 978:10, 981:14</p> <p>providers [1] - 888:7</p> <p>provides [4] - 833:9, 924:1, 976:22, 976:25</p> <p>proving [1] - 732:13</p> <p>provision [1] - 705:3</p> <p>psychiatric [1] - 701:24</p> <p>Psychiatric [2] - 702:4, 702:5</p> <p>psychiatry [1] - 701:15</p> <p>PTAB [1] - 753:11</p> <p>PTX [1] - 941:5</p> <p>PTX-005 [1] - 829:6</p> <p>PTX-098 [1] - 967:17</p> <p>PTX-153 [4] - 980:11, 980:21, 980:25, 981:2</p> <p>PTX-283 [4] - 849:16, 902:8, 902:13, 902:16</p> <p>PTX-299 [4] - 965:9, 965:19, 965:22, 965:25</p> <p>PTX-490 [3] - 900:15, 901:5, 901:8</p> <p>PTX-496 [1] - 900:14</p> <p>PTX-5 [2] - 830:5, 830:8</p> <p>PTX-793 [1] - 941:1</p> <p>PTX-8.7 [1] - 904:16</p> <p>PTX-811 [1] - 968:15</p> <p>PTX-816 [3] - 728:8, 864:21, 884:12</p> <p>PTX-829 [3] - 973:25, 974:4, 975:2</p> <p>PTX-830 [4] - 973:16, 974:7, 975:11,</p>	<p>975:15</p> <p>public [39] - 673:2, 674:15, 675:25, 676:5, 676:12, 678:4, 680:8, 682:12, 691:13, 691:14, 692:5, 692:8, 692:9, 692:12, 692:22, 692:23, 693:17, 695:8, 695:14, 695:24, 696:16, 699:14, 699:15, 733:10, 737:22, 751:22, 752:1, 752:18, 752:23, 756:1, 758:13, 759:6, 759:7, 761:15, 761:21, 785:10, 789:13, 943:10, 946:25</p> <p>publically [24] - 674:11, 674:12, 678:18, 689:8, 694:9, 694:20, 694:24, 734:1, 743:17, 751:15, 754:7, 754:12, 773:13, 788:24, 795:2, 881:12, 946:21, 948:3, 951:4, 952:1, 956:8, 956:15, 957:5, 972:12</p> <p>publication [29] - 681:17, 715:24, 731:22, 732:9, 737:18, 766:5, 779:3, 779:5, 807:23, 809:1, 810:5, 814:5, 818:25, 819:2, 820:1, 820:3, 827:5, 833:1, 833:4, 849:20, 849:23, 850:16, 928:2, 928:4, 938:12, 946:9, 947:25, 957:11, 957:17</p> <p>Publication [30] - 727:10, 727:16, 727:23, 728:5, 800:16, 800:17, 803:12, 803:16, 805:6, 805:15, 805:23, 806:5, 806:15, 806:23, 808:10, 810:8, 811:4, 813:11, 813:22, 814:7, 820:17, 820:18,</p>	<p>822:12, 822:13, 823:25, 824:4, 824:5, 827:1, 882:21, 883:1</p> <p>publications [3] - 778:23, 839:6, 848:4</p> <p>published [47] - 676:1, 676:14, 703:6, 703:9, 714:16, 715:16, 719:14, 725:21, 727:7, 731:24, 734:11, 734:16, 746:3, 746:20, 752:18, 752:22, 753:9, 754:10, 754:15, 754:19, 754:24, 779:7, 785:9, 789:13, 793:6, 835:4, 835:6, 837:21, 845:7, 852:18, 855:3, 860:4, 862:14, 864:13, 865:4, 865:7, 878:13, 888:11, 893:21, 927:24, 947:10, 947:13, 956:12, 959:7, 1000:8</p> <p>pull [16] - 744:23, 745:21, 745:22, 783:6, 826:3, 837:3, 837:17, 844:17, 850:20, 882:12, 884:12, 925:13, 981:23, 986:3, 990:20, 999:11</p> <p>pulled [7] - 741:17, 749:9, 752:7, 752:8, 752:10, 753:20, 768:14</p> <p>pulling [2] - 912:15, 923:9</p> <p>punt [1] - 948:15</p> <p>pure [10] - 680:6, 688:1, 688:25, 978:20, 997:20, 997:22, 999:24, 1000:1, 1000:2, 1000:14</p> <p>purified [3] - 978:16, 998:7, 998:8</p> <p>purify [3] - 977:13, 997:11, 997:12</p> <p>purity [12] - 680:7, 681:22, 978:15, 978:19, 978:21, 979:4, 999:21, 1000:10, 1000:19, 1000:21, 1000:24</p>
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<p>purple [4] - 809:13, 817:9, 818:18, 821:7</p> <p>purported [2] - 771:17, 894:12</p> <p>purporting [1] - 755:17</p> <p>purpose [7] - 674:14, 686:4, 732:2, 766:19, 774:21, 798:3, 835:14</p> <p>purposes [3] - 696:2, 765:10, 916:13</p> <p>pursuing [1] - 740:4</p> <p>push [3] - 741:13, 837:3, 837:17</p> <p>pushed [1] - 851:5</p> <p>put [46] - 673:13, 686:13, 688:16, 733:3, 743:14, 745:11, 761:8, 770:23, 770:25, 775:4, 775:10, 777:9, 790:12, 809:22, 815:23, 829:4, 830:9, 836:22, 850:11, 852:13, 860:1, 864:25, 865:16, 870:22, 872:14, 876:21, 876:24, 880:9, 886:11, 886:12, 893:15, 900:11, 917:13, 945:1, 947:3, 958:9, 966:17, 967:22, 968:18, 974:6, 975:18, 976:11, 981:2, 986:24, 988:24, 998:20</p> <p>putting [4] - 686:6, 844:21, 895:19, 987:10</p>	<p>qualifying [1] - 993:20</p> <p>quantitate [2] - 982:19, 982:22</p> <p>quantities [2] - 961:24, 996:24</p> <p>quantity [2] - 991:17, 993:4</p> <p>questioned [1] - 749:2</p> <p>questioning [1] - 947:2</p> <p>questions [12] - 672:14, 733:10, 790:12, 793:25, 796:12, 861:4, 882:9, 884:3, 886:9, 900:1, 937:22, 984:3</p> <p>queue [1] - 914:14</p> <p>quick [1] - 701:8</p> <p>quickly [3] - 716:5, 745:12, 874:9</p> <p>quite [15] - 692:17, 693:16, 712:7, 724:21, 745:12, 814:12, 833:25, 835:4, 854:5, 859:11, 898:6, 973:8, 979:2, 979:4, 996:18</p> <p>quote [4] - 761:14, 793:2, 952:9, 952:10</p> <p>quotes [1] - 789:18</p> <p>quoting [1] - 766:2</p>	<p>923:13, 923:15, 936:15</p> <p>ranging [1] - 739:4</p> <p>rapidly [1] - 875:8</p> <p>rather [7] - 691:19, 691:21, 738:10, 759:25, 853:20, 995:23, 997:16</p> <p>rats [5] - 838:24, 840:11, 863:11, 864:1, 864:4</p> <p>re [6] - 695:18, 831:9, 864:2, 864:7, 929:10</p> <p>RE [1] - 704:22</p> <p>re-entrainment [2] - 864:2, 864:7</p> <p>re-examined [1] - 929:10</p> <p>re-re [1] - 695:18</p> <p>RE604 [21] - 772:21, 800:10, 800:14, 801:17, 809:20, 816:12, 816:16, 817:10, 819:7, 819:16, 820:22, 821:3, 821:12, 821:20, 821:22, 822:15, 822:21, 822:23, 823:4, 827:5, 827:12</p> <p>reach [3] - 841:3, 843:2, 965:1</p> <p>reached [1] - 800:4</p> <p>react [1] - 675:12</p> <p>reacted [2] - 1001:19, 1001:20</p> <p>reacting [14] - 680:25, 942:18, 943:12, 943:15, 944:7, 947:15, 947:17, 947:21, 952:11, 952:14, 956:9, 956:16, 957:6, 972:11</p> <p>reaction [7] - 756:24, 831:10, 959:23, 960:9, 960:17, 962:19, 963:18</p> <p>reactions [1] - 942:25</p> <p>read [23] - 680:25, 681:1, 710:13, 758:23, 762:15, 778:15, 784:4, 784:16, 786:6, 786:12, 788:7, 795:20, 833:13, 891:1, 928:19, 928:23, 943:5, 943:7, 943:9, 947:21, 985:14,</p>	<p>988:19, 994:18</p> <p>reading [14] - 725:3, 728:4, 758:22, 781:20, 804:5, 806:3, 806:10, 806:21, 808:8, 809:8, 817:3, 988:11, 989:7, 1001:11</p> <p>reads [3] - 680:22, 681:5, 788:22</p> <p>ready [2] - 672:14, 777:18</p> <p>real [4] - 742:12, 771:16, 785:22, 894:9</p> <p>realize [1] - 946:8</p> <p>really [49] - 679:5, 679:6, 679:25, 708:22, 712:8, 715:25, 717:22, 726:7, 729:16, 732:2, 738:5, 738:17, 743:6, 750:14, 754:17, 755:21, 755:25, 757:1, 757:19, 771:25, 772:16, 797:25, 810:18, 810:25, 822:5, 826:12, 827:22, 835:15, 838:6, 885:16, 890:21, 891:12, 899:25, 900:2, 905:17, 907:5, 951:17, 955:9, 955:20, 966:11, 971:23, 972:8, 974:21, 976:5, 977:18, 978:6, 979:4, 985:23, 986:2</p> <p>realm [1] - 756:1</p> <p>reason [27] - 675:21, 678:20, 680:4, 681:8, 684:8, 691:4, 692:13, 697:10, 746:19, 750:7, 753:15, 753:22, 756:20, 761:6, 768:6, 772:23, 773:25, 775:22, 796:20, 807:5, 833:6, 841:1, 865:23, 866:1, 907:18, 907:22, 983:2</p> <p>reasonable [16] - 742:15, 801:14, 810:23, 811:14,</p>	<p>814:9, 878:17, 878:19, 878:25, 879:3, 879:6, 879:10, 879:13, 953:15, 953:22, 978:8, 979:24</p> <p>reasonably [2] - 749:2, 771:9</p> <p>reasons [7] - 735:15, 813:19, 819:15, 821:19, 899:19, 912:2, 918:9</p> <p>reboot [1] - 1003:20</p> <p>rebuttal [4] - 679:13, 689:19, 711:14, 895:15</p> <p>rebutting [1] - 938:2</p> <p>recap [1] - 707:14</p> <p>receipt [1] - 770:6</p> <p>received [2] - 692:20, 896:10</p> <p>receiving [1] - 808:23</p> <p>recent [5] - 763:16, 764:8, 929:10, 932:13, 933:17</p> <p>recently [5] - 782:24, 784:3, 787:2, 787:9, 849:21</p> <p>receptor [6] - 812:4, 831:10, 831:12, 860:23, 863:24, 873:20</p> <p>receptors [18] - 710:3, 722:5, 726:8, 727:17, 799:20, 810:10, 857:10, 857:13, 857:14, 857:15, 857:16, 857:18, 857:20, 858:1, 858:10, 858:23, 932:8</p> <p>recess [3] - 776:23, 828:14, 895:12</p> <p>recited [2] - 682:12, 922:9</p> <p>recognize [28] - 683:4, 712:25, 714:2, 715:2, 716:8, 716:16, 716:22, 717:3, 719:2, 720:6, 721:10, 724:15, 725:8, 726:15, 728:10, 729:23, 731:4, 778:8, 798:11, 910:22, 917:16, 920:9, 957:16, 965:11, 973:17, 975:3, 980:12, 994:5</p> <p>recognized [2] -</p>
<p>Q</p>	<p>R</p>			
<p>Q3A [3] - 944:24, 953:6, 973:8</p> <p>QC [1] - 780:4</p> <p>qualification [6] - 853:22, 995:19, 995:22, 996:3, 996:12, 997:16</p> <p>qualifications [2] - 700:15, 705:14</p> <p>qualified [1] - 898:19</p> <p>qualifies [3] - 734:25, 737:11, 765:5</p> <p>qualify [5] - 705:20, 754:13, 764:13, 766:8, 795:3</p>	<p>raised [3] - 694:16, 861:3, 938:14</p> <p>raises [2] - 757:18, 861:3</p> <p>Rajaratnam [9] - 728:13, 728:24, 730:12, 799:3, 799:6, 799:8, 860:8, 885:13, 885:22</p> <p>Rajaratnam's [1] - 885:10</p> <p>Rajaratnam [9] - 728:18, 864:13, 864:22, 865:16, 866:15, 870:4, 883:11, 884:9</p> <p>ramelteon [6] - 861:23, 862:19, 862:22, 864:1, 864:8, 874:18</p> <p>range [12] - 723:11, 807:2, 812:19, 853:23, 873:13, 876:18, 896:22, 898:6, 919:25,</p>			

<p>752:1, 993:17 recollection [2] - 771:21, 775:19 recommend [1] - 945:19 recommendation [2] - 909:10, 920:3 recommendations [2] - 919:24, 981:14 recommended [4] - 723:4, 723:6, 829:20, 874:18 record [35] - 687:17, 687:25, 688:1, 691:22, 736:21, 738:19, 739:1, 744:17, 762:16, 765:15, 771:23, 774:25, 783:20, 784:5, 786:13, 786:15, 786:16, 787:19, 787:21, 788:22, 794:24, 797:17, 798:7, 804:4, 805:14, 807:10, 816:18, 818:7, 893:19, 934:12, 939:16, 948:17, 951:11, 958:24, 1000:8 records [1] - 762:24 Records [4] - 784:11, 784:17, 786:6, 786:12 recross [1] - 695:18 recruiting [3] - 746:25, 757:23, 770:5 Red [1] - 962:11 red [1] - 871:25 Red-AI [1] - 962:11 redirect [13] - 674:12, 690:20, 690:22, 691:15, 695:9, 699:8, 699:18, 882:10, 935:24, 946:23, 949:9, 949:15, 956:11 REDIRECT [2] - 882:18, 936:1 reduce [5] - 848:8, 907:15, 914:7, 931:16, 997:13 reduced [5] - 718:5, 962:17, 1001:16, 1001:19, 1001:20 reducing [12] - 912:7, 942:11, 951:14, 952:2, 954:1, 956:17, 957:7,</p>	<p>960:11, 960:12, 962:7, 963:17, 964:1 reduction [3] - 680:23, 690:6, 960:14 refer [6] - 846:15, 865:13, 866:6, 890:23, 916:18, 957:18 Reference [5] - 932:20, 932:23, 933:8, 933:12 reference [39] - 673:14, 673:16, 673:25, 674:18, 690:22, 695:12, 697:17, 712:20, 713:24, 714:23, 724:11, 761:16, 761:17, 781:7, 794:15, 799:14, 801:11, 814:4, 816:8, 817:25, 855:23, 879:19, 905:24, 931:23, 931:24, 949:18, 957:18, 957:19, 957:21, 957:24, 958:11, 971:5, 971:17, 976:16, 976:17, 982:8, 998:22, 999:24, 1000:20 referenced [3] - 815:13, 818:8, 965:5 references [23] - 746:2, 800:16, 801:13, 803:13, 805:21, 808:25, 809:25, 810:20, 810:22, 811:21, 813:15, 814:3, 814:8, 819:13, 819:24, 854:15, 872:9, 877:22, 905:23, 972:25, 973:6, 973:13, 974:12 References [3] - 746:11, 792:11, 792:15 referral [1] - 797:19 referred [5] - 708:14, 802:9, 868:24, 904:13, 906:22 referring [10] - 788:15, 788:16, 788:19, 864:12, 901:2, 919:12, 929:5, 960:6, 970:24, 988:12</p>	<p>refers [8] - 720:24, 725:23, 850:21, 854:23, 868:2, 877:6, 880:20, 916:23 refining [1] - 717:22 reflect [2] - 738:22, 770:5 reflected [1] - 766:25 reflecting [1] - 739:13 reflection [1] - 748:20 reflects [5] - 748:4, 749:5, 767:5, 790:8, 795:16 reflex [1] - 892:6 regard [8] - 704:15, 730:23, 945:2, 972:22, 973:12, 979:11, 979:15, 981:25 regarding [9] - 704:10, 761:13, 800:13, 807:24, 820:4, 922:24, 948:23, 976:12, 980:16 regardless [2] - 996:3, 996:14 regards [1] - 722:16 regime [1] - 918:7 Register [3] - 752:22, 753:10, 753:13 regulating [2] - 805:8, 805:9 regulations [1] - 747:5 regulatory [4] - 695:13, 699:14, 955:19, 993:13 reiterate [1] - 813:20 rejected [2] - 974:10, 975:21 rejection [1] - 975:22 relapse [1] - 806:7 relate [1] - 921:25 related [6] - 888:13, 954:7, 955:1, 982:13, 984:25 relates [2] - 704:19, 881:3 relating [1] - 866:2 relation [1] - 870:7 relationship [5] - 681:10, 789:10, 862:6, 922:24 relative [9] - 807:19, 837:4, 844:3, 859:1, 860:22, 867:18, 971:10, 978:25, 979:2 relatively [4] - 723:11,</p>	<p>847:5, 953:18, 978:25 release [3] - 869:16, 873:25, 874:12 relevance [5] - 673:19, 751:14, 751:18, 771:21, 795:1 relevant [11] - 674:2, 692:21, 704:3, 737:3, 740:11, 750:24, 752:13, 754:6, 800:9, 857:16, 955:19 reliable [3] - 925:24, 926:10, 990:12 relied [12] - 673:16, 704:18, 756:14, 765:13, 765:22, 785:24, 790:22, 820:9, 820:11, 822:5, 823:12, 973:1 rely [26] - 704:9, 704:14, 713:5, 714:7, 715:7, 717:8, 719:6, 720:11, 721:15, 723:20, 724:19, 725:12, 726:21, 728:15, 730:3, 766:23, 769:3, 796:25, 798:15, 819:22, 820:6, 822:2, 854:15, 876:7, 877:22, 881:17 relying [6] - 740:22, 746:1, 765:7, 765:8, 765:9, 765:11 REM [1] - 858:11 remain [5] - 736:25, 777:23, 806:1, 892:2, 949:23 remained [1] - 913:21 remaining [2] - 817:23, 904:24 remains [2] - 841:2, 917:23 remember [13] - 673:8, 674:8, 684:22, 687:4, 695:4, 699:9, 738:13, 759:24, 794:3, 827:3, 891:15, 900:14, 917:5 reminds [1] - 870:14 remove [3] - 697:1, 764:24, 977:18 removed [2] - 688:23, 999:20 rendering [5] -</p>	<p>957:24, 965:17, 973:22, 975:8, 980:19 renew [3] - 787:23, 787:25, 948:17 repeatedly [1] - 785:19 repeating [1] - 772:6 reply [3] - 711:10, 711:16, 936:22 report [56] - 678:1, 678:22, 697:4, 697:8, 697:18, 697:23, 697:25, 698:2, 698:6, 698:14, 698:15, 733:15, 733:20, 733:22, 734:3, 736:1, 736:7, 742:5, 758:5, 759:16, 775:17, 781:14, 781:21, 785:1, 785:6, 785:7, 785:23, 786:4, 788:3, 788:5, 788:7, 788:16, 820:9, 820:11, 822:5, 851:15, 902:21, 930:13, 938:8, 939:6, 939:7, 939:22, 940:23, 940:24, 941:1, 941:5, 941:18, 941:19, 942:15, 942:17, 945:14, 961:11, 964:16, 966:22 reported [7] - 683:19, 848:4, 864:4, 870:6, 900:4, 979:1, 987:5 Reporter [1] - 895:9 reporter [2] - 896:16, 998:13 REPORTER'S [1] - 672:3 reporting [5] - 867:1, 870:15, 936:14, 993:21, 994:19 reports [14] - 674:17, 679:2, 681:18, 699:21, 704:5, 710:14, 734:4, 735:22, 765:13, 862:22, 914:21, 938:17, 938:19, 957:22 represent [3] - 707:6, 707:7, 707:9 representation [1] - 757:9</p>
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<p>represented [2] - 737:11, 772:7</p> <p>representing [2] - 708:12, 916:1</p> <p>represents [3] - 769:3, 801:22, 939:21</p> <p>reprocessing [1] - 890:3</p> <p>require [3] - 679:19, 790:7, 824:21</p> <p>required [4] - 706:20, 747:4, 759:6, 759:8</p> <p>requirement [4] - 690:24, 824:12, 955:20, 955:21</p> <p>requirements [2] - 680:7, 993:13</p> <p>requires [4] - 691:19, 692:25, 820:5, 955:10</p> <p>requiring [1] - 823:7</p> <p>Research [2] - 702:7, 959:13</p> <p>research [17] - 702:8, 702:13, 702:25, 703:9, 713:3, 714:5, 719:5, 728:13, 858:18, 860:22, 861:2, 896:6, 918:15, 923:17, 933:17, 933:20, 959:23</p> <p>researcher [5] - 829:16, 839:22, 887:17, 896:6, 896:20</p> <p>researchers [4] - 708:16, 835:18, 866:15, 870:5</p> <p>researching [2] - 858:16, 897:14</p> <p>reset [25] - 709:3, 709:4, 709:11, 709:19, 712:17, 713:21, 715:22, 727:18, 728:20, 746:14, 779:6, 810:12, 827:9, 827:15, 833:2, 836:12, 844:10, 846:6, 846:12, 869:15, 897:17, 897:24, 898:7, 936:17, 936:20</p> <p>resets [1] - 836:9</p> <p>resetting [16] - 707:23, 709:15, 709:24, 710:7, 712:14, 713:16, 803:25, 804:1,</p>	<p>805:10, 814:24, 833:24, 843:12, 844:13, 848:14, 870:13</p> <p>residency [3] - 701:24, 887:3, 887:4</p> <p>residents [1] - 701:18</p> <p>resolve [8] - 738:9, 738:11, 771:19, 772:4, 772:5, 772:10, 772:11, 775:20</p> <p>resolved [1] - 772:3</p> <p>resonance [1] - 990:4</p> <p>resource [1] - 737:22</p> <p>respect [3] - 736:17, 736:24, 972:22</p> <p>respected [1] - 928:4</p> <p>respectfully [2] - 711:25, 942:24</p> <p>respond [11] - 687:14, 711:2, 795:6, 889:19, 935:5, 939:8, 974:18, 975:25, 976:3, 982:17, 983:14</p> <p>responding [4] - 895:5, 941:20, 975:20, 981:7</p> <p>response [36] - 728:22, 759:10, 759:16, 833:23, 835:1, 835:7, 835:8, 835:24, 837:9, 837:14, 837:24, 841:4, 841:15, 870:7, 889:5, 889:11, 889:13, 898:25, 905:6, 912:6, 912:9, 912:23, 916:24, 921:5, 941:1, 956:10, 961:2, 973:20, 974:24, 975:6, 976:8, 980:8, 980:15, 981:4, 981:6, 982:17</p> <p>responses [3] - 761:12, 899:10, 908:10</p> <p>responsive [1] - 751:13</p> <p>responsivity [1] - 889:3</p> <p>rest [3] - 841:24, 864:2, 890:9</p> <p>result [9] - 685:3, 707:23, 708:1, 709:14, 779:6, 843:17, 858:7,</p>	<p>869:24, 906:17</p> <p>resulted [2] - 729:1, 832:17</p> <p>resulting [4] - 817:21, 830:23, 911:23, 911:24</p> <p>results [25] - 715:18, 739:13, 739:17, 740:6, 746:21, 756:10, 758:4, 779:9, 826:14, 827:9, 833:1, 833:4, 856:7, 856:8, 864:4, 867:1, 871:10, 885:11, 905:4, 911:14, 921:4, 925:21, 927:17, 930:7, 936:15</p> <p>resume [1] - 1002:15</p> <p>retained [1] - 888:20</p> <p>retention [2] - 971:10, 986:8</p> <p>retook [2] - 777:21, 949:22</p> <p>retiral [1] - 759:25</p> <p>retrieve [1] - 785:15</p> <p>revealed [1] - 988:19</p> <p>reveals [1] - 695:12</p> <p>reversed [2] - 676:19, 944:19</p> <p>reversible [4] - 889:2, 889:6, 889:10, 891:11</p> <p>reverted [1] - 909:3</p> <p>review [22] - 704:1, 720:9, 720:20, 720:25, 721:13, 721:24, 730:1, 730:15, 798:14, 798:24, 829:8, 835:14, 835:17, 860:4, 872:11, 930:24, 931:2, 931:4, 934:22, 934:25, 936:8, 973:11</p> <p>reviewed [7] - 722:12, 785:9, 788:8, 789:12, 928:2, 965:16, 980:18</p> <p>reviewing [7] - 720:21, 720:22, 721:25, 798:25, 799:1, 838:22, 860:8</p> <p>revise [1] - 686:3</p> <p>reward [1] - 995:10</p> <p>RFP [1] - 759:5</p> <p>rhythm [68] - 700:18, 702:23, 702:25, 703:7, 704:25,</p>	<p>706:2, 706:3, 706:4, 706:7, 706:8, 706:14, 706:16, 706:17, 706:18, 706:23, 707:15, 708:17, 708:21, 708:25, 709:6, 710:5, 712:1, 713:21, 713:23, 720:23, 722:7, 722:11, 722:13, 722:19, 724:5, 725:1, 726:11, 727:24, 728:1, 729:6, 730:18, 789:10, 799:17, 799:24, 805:12, 810:17, 811:3, 812:5, 812:8, 814:13, 815:1, 822:25, 837:3, 837:7, 839:3, 844:8, 844:9, 847:4, 847:12, 848:14, 850:20, 862:3, 862:4, 862:7, 863:11, 883:2, 897:7, 897:10, 898:20, 900:5, 909:6, 925:24, 931:15</p> <p>Rhythm [1] - 918:21</p> <p>rhythms [31] - 706:5, 706:11, 707:16, 708:5, 726:10, 804:11, 805:8, 805:10, 851:1, 851:4, 854:22, 862:15, 896:6, 896:21, 897:1, 897:3, 925:23, 926:24, 927:9, 927:10, 927:20, 928:15, 928:22, 929:3, 929:11, 930:9, 932:15, 934:2, 935:10, 937:7</p> <p>Rifampin [1] - 821:24</p> <p>RIFKIND [1] - 671:8</p> <p>right-hand [10] - 763:22, 778:6, 840:20, 860:19, 884:14, 925:20, 926:3, 930:6, 968:6, 970:13</p> <p>rights [2] - 687:5, 687:12</p> <p>rise [2] - 689:4, 850:25</p> <p>rises [1] - 898:9</p> <p>risk [2] - 772:6, 868:16</p>	<p>Robert [3] - 702:17, 715:5, 926:15</p> <p>robust [1] - 851:25</p> <p>role [6] - 772:19, 858:6, 858:10, 858:11, 897:17, 897:19</p> <p>roles [1] - 676:19</p> <p>Rolfe [2] - 1:24, 1004:2</p> <p>room [1] - 941:17</p> <p>rotation [2] - 979:2, 979:3</p> <p>roughly [2] - 869:12, 869:25</p> <p>Route [2] - 959:14, 961:18</p> <p>route [7] - 755:1, 959:23, 960:1, 961:7, 961:23, 995:19, 1001:15</p> <p>row [2] - 987:24, 994:12</p> <p>rows [1] - 994:12</p> <p>ROZENDAAL [79] - 671:3, 672:7, 672:18, 673:3, 673:11, 673:24, 674:5, 677:24, 678:11, 679:3, 679:22, 680:18, 680:21, 681:3, 681:6, 681:13, 681:15, 687:14, 687:16, 689:11, 690:15, 691:3, 692:16, 692:20, 693:24, 694:5, 694:10, 695:6, 695:11, 698:2, 698:9, 698:18, 698:22, 699:12, 894:14, 939:4, 939:12, 939:19, 941:4, 941:12, 942:22, 945:8, 945:12, 946:15, 947:23, 948:6, 948:12, 948:16, 949:3, 949:17, 951:6, 951:9, 952:5, 952:18, 956:19, 957:2, 958:3, 958:14, 960:21, 960:24, 961:12, 964:13, 965:20, 972:14, 974:2, 975:13, 980:23, 984:11, 984:14, 998:14, 998:17,</p>
--	--	---	--	---

<p>998:19, 999:8, 999:11, 999:13, 1001:25, 1002:21, 1003:1, 1003:13 Rozendaal [8] - 696:23, 698:1, 773:15, 773:23, 938:14, 939:3, 939:14, 943:16 rozendaal [1] - 741:17 Rozendaal's [2] - 944:3, 944:5 RPR [2] - 1:24, 1004:2 RRT [1] - 970:4 RRTs [3] - 969:20, 969:21, 969:24 rule [3] - 750:21, 750:24, 770:19 Rule [5] - 678:8, 697:5, 738:5, 748:9, 749:12 ruled [1] - 951:11 rules [4] - 686:5, 742:18, 770:17, 771:2 ruling [2] - 948:14, 956:21 rummaging [2] - 688:21, 688:22 run [3] - 683:15, 740:8, 740:9 running [21] - 708:15, 804:11, 838:23, 844:2, 852:21, 854:22, 863:11, 908:15, 925:22, 926:9, 926:24, 927:10, 927:19, 928:14, 928:21, 929:3, 929:11, 930:9, 930:13, 932:15, 934:2</p>	<p>926:15, 927:17, 929:6, 929:7, 929:21, 930:2, 930:20, 932:23, 935:11, 937:8 Sack's [2] - 840:3, 891:17 Sacks [1] - 886:23 safe [1] - 941:15 safety [5] - 995:22, 996:3, 996:15, 996:18, 997:16 Safety [2] - 778:17, 789:18 salt [1] - 962:12 sample [3] - 986:24, 986:25, 987:4 samples [2] - 868:3, 982:25 sandbagged [1] - 756:18 sat [1] - 751:6 satisfied [2] - 680:7, 748:10 satisfies [2] - 1000:10, 1000:12 satisfy [2] - 749:7, 771:1 saw [5] - 683:2, 739:8, 764:9, 776:1, 822:22 scale [2] - 900:1, 917:3 schedule [2] - 672:11, 885:7 scheduling [1] - 672:9 schematic [2] - 707:3, 707:6 scheme [8] - 821:1, 959:23, 960:9, 960:17, 962:20, 963:18, 963:24, 964:2 school [4] - 701:23, 886:15, 886:17, 886:18 School [2] - 702:15, 896:4 science [1] - 898:20 Science [2] - 701:16, 701:25 sciences [1] - 896:11 scientist [1] - 857:19 scientists [1] - 677:12 SCN [1] - 932:8 scope [3] - 750:23, 801:3, 881:15 score [6] - 943:16, 943:21, 943:23, 944:10, 944:15, 944:16</p>	<p>screen [24] - 723:3, 783:2, 787:18, 790:18, 791:2, 791:20, 792:3, 792:10, 795:10, 846:4, 857:3, 872:15, 893:16, 925:14, 950:7, 958:9, 966:18, 967:22, 968:18, 968:24, 974:6, 975:18, 981:2, 994:6 screenshot [13] - 763:12, 765:16, 766:22, 767:5, 767:6, 767:8, 767:14, 768:25, 771:17, 771:18, 775:4, 775:6, 776:1 screenshots [1] - 762:23 scroll [6] - 783:18, 786:21, 787:7, 791:6, 791:24, 792:7 search [2] - 783:14, 783:17 seat [2] - 776:24, 777:24 second [32] - 687:22, 698:9, 700:9, 706:7, 709:2, 732:5, 753:4, 753:15, 753:22, 774:3, 805:18, 807:3, 811:18, 851:20, 851:21, 852:16, 897:23, 906:11, 914:9, 918:7, 918:18, 927:15, 929:1, 932:1, 951:21, 969:4, 978:12, 979:11, 980:10, 981:10, 984:23, 989:20 second-to-last [1] - 918:18 second-to-the-last [1] - 980:10 secondary [4] - 711:11, 789:9, 801:7, 980:4 secrete [1] - 867:25 secreting [1] - 867:22 section [36] - 727:9, 740:17, 741:11, 746:11, 755:8, 785:11, 788:9, 788:13, 789:15, 791:17, 791:20, 791:25, 792:2,</p>	<p>816:19, 817:4, 826:23, 838:12, 845:19, 847:21, 873:17, 885:1, 926:4, 926:22, 927:7, 927:14, 927:16, 930:6, 931:20, 933:2, 959:12, 961:15, 962:1, 963:2, 963:6, 974:7, 984:24 Section [3] - 764:22, 843:21, 961:20 sections [1] - 911:10 sedative [1] - 708:22 sedatives [1] - 710:6 see [141] - 672:13, 672:15, 673:1, 678:22, 683:15, 691:9, 694:15, 698:14, 699:22, 708:9, 725:23, 727:10, 729:9, 737:20, 740:20, 741:23, 742:9, 742:12, 743:5, 744:18, 746:15, 747:8, 748:22, 758:22, 762:18, 763:3, 763:21, 768:24, 769:24, 774:12, 778:4, 778:22, 779:2, 779:18, 779:23, 780:12, 780:19, 781:1, 781:7, 783:20, 786:8, 786:9, 786:24, 787:17, 789:6, 791:10, 792:10, 792:14, 792:17, 802:2, 808:3, 809:3, 812:3, 819:8, 821:11, 823:15, 826:25, 828:1, 839:5, 840:22, 842:19, 845:19, 846:3, 857:4, 861:10, 863:9, 864:1, 866:12, 875:5, 875:10, 883:22, 885:3, 890:8, 893:16, 898:13, 900:16, 900:17, 900:25, 902:20, 906:6, 908:14, 908:16, 909:1, 909:5, 909:22, 909:23, 912:21, 913:17,</p>	<p>916:7, 918:24, 919:12, 919:15, 923:11, 925:20, 926:22, 926:25, 927:21, 929:15, 929:22, 930:10, 930:15, 931:5, 931:7, 931:12, 931:17, 932:5, 932:11, 932:16, 933:6, 933:9, 933:11, 933:17, 933:18, 933:23, 934:3, 934:20, 934:23, 935:4, 935:6, 935:13, 935:17, 937:1, 937:13, 940:1, 941:7, 951:22, 959:12, 962:14, 968:14, 971:5, 971:17, 981:3, 982:8, 985:3, 986:5, 987:12, 987:25, 988:8, 990:19, 995:21, 999:18 seeing [6] - 672:21, 688:23, 785:2, 904:16, 907:12, 945:14 seem [3] - 674:21, 781:13, 867:16 sees [1] - 745:19 selected [1] - 911:10 self [4] - 745:3, 795:10, 795:16, 939:7 self-authenticating [3] - 745:3, 795:10, 795:16 self-contradictory [1] - 939:7 senior [1] - 904:12 sense [5] - 682:23, 757:1, 834:6, 862:10, 1003:4 sensitivity [1] - 857:10 sensor [1] - 890:3 sent [2] - 934:18, 936:12 sentence [9] - 676:9, 927:15, 928:13, 929:9, 931:5, 933:3, 944:2, 964:7, 984:23 sentences [1] - 964:8 separate [6] - 737:10, 769:9, 940:9, 991:22, 992:2, 992:10 separately [2] -</p>
<p>S</p>				
<p>S-I-N-G-H [1] - 673:15 S-K-E-N-E [1] - 903:22 Sack [36] - 702:17, 715:5, 715:16, 715:18, 715:21, 718:7, 839:20, 839:22, 849:25, 851:14, 851:24, 886:24, 886:25, 887:7, 888:9, 897:12, 897:13, 902:1, 902:2, 902:4, 902:11, 902:20, 910:25, 916:6, 919:14, 919:23,</p>				

<p>801:24, 983:22 separation [1] - 992:9 September [5] - 740:19, 744:8, 767:24, 768:4, 941:4 sequential [1] - 1001:24 series [5] - 686:16, 716:3, 909:23, 910:2, 910:6 serotonin [1] - 862:11 served [1] - 761:11 set [26] - 681:17, 681:18, 695:21, 700:13, 746:14, 761:12, 779:6, 816:5, 819:13, 819:24, 827:9, 827:15, 833:2, 844:12, 844:14, 845:24, 846:6, 846:8, 880:5, 897:17, 897:24, 905:4, 916:9, 936:17, 936:19, 987:22 sets [1] - 977:4 setting [1] - 925:9 seven [8] - 846:16, 904:19, 904:23, 922:21, 926:23, 967:20, 969:8, 969:15 seventh [1] - 718:10 several [9] - 682:2, 700:5, 776:9, 794:9, 847:5, 896:25, 908:22, 918:22, 929:10 shall [1] - 796:9 Shasun [1] - 688:6 SHAW [1] - 671:2 shed [1] - 740:2 sheet [6] - 745:22, 762:18, 762:25, 763:3, 763:13, 966:9 shift [42] - 709:11, 709:15, 713:21, 728:21, 729:1, 729:11, 729:12, 729:16, 729:17, 730:17, 812:5, 842:22, 843:18, 851:2, 851:11, 869:21, 871:17, 877:12, 883:12, 883:14, 883:17, 883:19, 883:22, 884:7, 884:19, 885:17, 885:19,</p>	<p>885:22, 897:2, 913:3, 913:7, 915:19, 920:19, 921:6, 921:7, 921:12, 921:14, 922:25, 923:1, 923:2, 923:3 shifted [3] - 870:8, 871:16, 875:8 shifting [25] - 713:16, 728:22, 814:23, 850:21, 850:25, 851:8, 858:10, 862:23, 870:11, 870:17, 871:10, 874:22, 875:8, 875:17, 876:16, 877:4, 877:5, 885:16, 899:9, 908:12, 921:10, 922:7, 924:13, 932:7, 932:13 shifts [11] - 718:15, 718:19, 722:9, 810:13, 813:24, 838:4, 838:8, 853:25, 854:1, 869:24, 921:17 short [2] - 862:13, 874:4 shorten [1] - 924:17 shortened [2] - 875:3, 908:24 shortly [1] - 907:24 shortness [1] - 963:10 shove [1] - 741:13 show [25] - 674:14, 682:23, 687:17, 736:1, 751:1, 751:3, 752:24, 755:13, 756:9, 766:20, 786:1, 786:15, 804:21, 881:8, 902:24, 904:22, 907:2, 907:4, 925:21, 930:7, 938:12, 940:23, 970:18 showed [12] - 688:8, 702:18, 715:21, 755:18, 804:24, 839:9, 855:16, 884:19, 899:18, 903:9, 906:18, 989:12 showing [8] - 705:13, 711:24, 863:1, 909:24, 916:3, 920:23, 966:2, 967:24</p>	<p>shown [33] - 684:10, 723:5, 795:1, 813:25, 830:22, 832:16, 832:23, 833:2, 838:23, 839:2, 863:10, 863:13, 882:2, 890:4, 897:6, 906:23, 913:16, 922:14, 922:18, 923:20, 924:4, 928:14, 928:21, 931:15, 932:2, 934:1, 938:24, 950:7, 963:14, 967:9, 970:7, 970:10, 977:2 shows [8] - 747:3, 749:17, 770:8, 836:25, 837:1, 837:9, 912:2, 926:8 shy [2] - 935:15, 937:15 shying [1] - 937:18 sic [1] - 679:8 sic [1] - 702:6 side [23] - 677:23, 734:15, 770:23, 807:8, 807:9, 824:18, 840:20, 843:17, 884:14, 894:8, 900:17, 907:15, 907:20, 912:17, 914:8, 939:22, 943:21, 943:23, 944:16, 970:12, 970:13 sidebar [3] - 951:22, 951:23, 952:23 sides [2] - 699:21, 947:14 sighted [4] - 826:17, 867:18, 905:9, 905:13 significance [6] - 715:25, 788:12, 904:4, 904:8, 906:24, 966:10 significant [8] - 865:13, 870:17, 871:20, 871:24, 877:13, 884:19, 953:19, 978:22 significantly [2] - 841:7, 870:8 similar [10] - 799:21, 813:19, 813:23, 820:20, 822:23, 837:15, 887:7, 916:6, 970:15, 973:8</p>	<p>similarities [1] - 822:20 similarly [6] - 711:12, 811:4, 841:11, 951:3, 953:16, 955:9 simpler [1] - 977:10 simplest [1] - 755:1 simply [18] - 674:7, 676:15, 678:17, 683:4, 686:2, 686:25, 690:5, 692:3, 696:20, 699:10, 706:3, 706:18, 742:5, 764:16, 785:16, 912:13, 963:21, 977:11 Singh [34] - 673:15, 941:21, 942:2, 942:3, 942:5, 942:8, 942:9, 942:11, 942:18, 942:20, 943:11, 943:13, 943:14, 944:6, 944:14, 944:24, 945:19, 946:9, 946:11, 946:13, 946:19, 947:2, 947:10, 947:13, 948:24, 949:18, 952:11, 952:13, 957:19, 957:21, 957:24, 958:12, 964:20 single [6] - 693:6, 815:22, 920:18, 922:7, 923:3, 924:14 sit [1] - 772:13 site [2] - 738:21, 747:11 sites [3] - 885:4, 897:20, 897:23 sitting [1] - 950:9 situation [1] - 752:6 Siva [1] - 958:12 Six [1] - 891:5 six [5] - 754:11, 762:22, 789:1, 797:6, 902:22 six-month [2] - 789:1, 797:6 Six-Pack [1] - 891:5 Skeme [1] - 917:14 SKEME [1] - 917:14 Skene [4] - 720:9, 903:22, 930:23, 931:22 skill [40] - 705:11, 705:17, 705:20, 709:23, 722:21,</p>	<p>753:12, 801:4, 802:6, 802:8, 802:21, 809:23, 810:23, 811:8, 811:13, 813:14, 814:9, 852:2, 879:5, 883:6, 885:25, 891:1, 891:6, 893:10, 953:24, 954:4, 954:8, 954:12, 954:15, 954:17, 954:21, 954:23, 955:9, 955:11, 955:25, 977:22, 991:21, 992:11, 993:7 skilled [4] - 729:4, 833:10, 840:10, 853:19 skip [4] - 800:3, 864:20, 914:17, 917:2 skipped [2] - 817:12, 870:14 sleep [119] - 700:17, 700:18, 701:19, 702:23, 703:1, 703:7, 704:25, 706:15, 706:17, 706:18, 706:20, 706:21, 706:23, 707:8, 707:9, 707:13, 707:17, 708:6, 708:11, 708:17, 708:21, 708:23, 709:6, 713:23, 720:23, 722:7, 722:11, 722:13, 722:19, 724:5, 726:11, 727:24, 728:1, 728:22, 728:23, 729:6, 730:19, 789:3, 789:7, 789:11, 799:17, 799:24, 802:3, 802:11, 802:22, 803:2, 803:4, 804:13, 804:16, 804:22, 804:25, 805:9, 805:19, 810:17, 811:5, 812:9, 814:14, 815:1, 815:3, 830:23, 832:17, 844:3, 844:9, 844:12, 855:14, 855:18, 855:21, 855:24, 856:7, 856:8, 858:11, 860:23, 868:22,</p>
---	---	---	---	--

<p>875:3, 880:20, 882:23, 883:2, 885:6, 885:7, 885:13, 887:2, 887:5, 887:16, 887:20, 887:22, 887:25, 888:2, 888:5, 888:6, 888:7, 888:13, 888:25, 889:2, 889:8, 890:4, 890:5, 890:15, 890:17, 891:15, 891:20, 891:23, 892:10, 892:11, 892:12, 892:13, 892:18, 892:23, 893:4, 893:6, 896:7, 901:15, 931:16, 934:22, 936:7, 936:13</p> <p>Sleep^[15] - 702:6, 702:7, 702:24, 703:11, 723:2, 723:17, 778:19, 783:16, 789:20, 816:11, 818:9, 829:9, 900:23, 918:22, 931:11</p> <p>sleep-related^[2] - 888:13</p> <p>Sleep/Wake^[9] - 778:19, 783:16, 789:20, 816:11, 818:9, 829:9, 900:23, 918:22, 931:11</p> <p>Sleep/Wake^[5] - 804:13, 804:16, 805:9, 805:19, 885:7</p> <p>Sleep/Wake^[2] - 700:19, 803:21</p> <p>sleepiness^[7] - 802:17, 802:18, 802:23, 848:9, 867:11, 892:18, 915:11</p> <p>sleeping^[2] - 890:23, 891:1</p> <p>sleepy^[4] - 892:14, 892:15, 915:13, 915:21</p> <p>slept^[3] - 803:1, 803:6, 856:3</p> <p>slew^[1] - 890:22</p> <p>Slide^[12] - 873:10, 915:25, 954:20, 967:17, 968:3, 970:8, 973:3, 976:24, 977:2, 977:24, 979:13,</p>	<p>981:23</p> <p>slide^[31] - 703:21, 705:13, 706:24, 708:10, 804:4, 804:18, 805:3, 807:14, 808:18, 812:11, 824:18, 886:13, 898:24, 899:11, 907:9, 908:1, 909:17, 911:8, 913:17, 914:10, 923:22, 950:19, 951:25, 953:7, 965:24, 970:12, 976:11, 979:10, 981:22, 981:24, 983:11</p> <p>slides^[7] - 752:17, 801:21, 815:5, 826:3, 873:7, 879:16, 976:11</p> <p>slight^[2] - 837:12, 837:15</p> <p>slightly^[4] - 867:13, 868:22, 871:14, 960:24</p> <p>slope^[1] - 909:1</p> <p>small^[7] - 684:5, 843:18, 909:23, 910:4, 913:10, 913:14, 923:14</p> <p>smaller^[8] - 840:24, 849:8, 853:25, 875:11, 906:16, 910:11, 914:13, 922:13</p> <p>snapshot^[4] - 746:17, 760:9, 760:11, 860:11</p> <p>snapshots^[1] - 735:5</p> <p>sneak^[1] - 680:1</p> <p>snippets^[1] - 686:16</p> <p>so-called^[8] - 794:15, 835:14, 838:4, 848:5, 849:9, 854:13, 881:3, 931:11</p> <p>so..^[1] - 690:16</p> <p>soccer^[1] - 865:23</p> <p>Society^[1] - 702:7</p> <p>sold^[1] - 687:11</p> <p>sole^[2] - 674:14, 788:6</p> <p>solely^[1] - 681:23</p> <p>solvent^[1] - 999:19</p> <p>someone^[27] - 675:21, 676:1, 683:14, 685:21, 686:6, 734:12, 750:9, 811:10,</p>	<p>829:15, 831:23, 833:16, 839:20, 841:23, 844:11, 844:16, 847:3, 878:9, 878:24, 891:7, 915:13, 921:13, 921:18, 921:23, 954:16, 955:18, 993:2, 993:3</p> <p>sometimes^[7] - 745:11, 745:12, 840:23, 868:24, 911:20, 912:8, 924:5</p> <p>somewhat^[6] - 705:16, 855:1, 893:25, 922:15, 954:16, 977:10</p> <p>soon^[1] - 839:18</p> <p>soporific^[2] - 848:13, 874:24</p> <p>sorry^[51] - 680:24, 692:20, 702:4, 718:22, 732:6, 744:16, 762:18, 764:18, 764:21, 772:25, 779:12, 779:15, 784:23, 786:19, 805:14, 814:6, 827:11, 827:13, 833:19, 848:22, 856:19, 856:20, 856:21, 859:17, 876:23, 880:11, 881:2, 886:25, 916:15, 928:18, 931:25, 936:24, 941:5, 941:15, 943:24, 945:4, 949:12, 950:18, 951:21, 954:2, 956:23, 966:20, 970:8, 976:2, 982:5, 984:5, 993:23, 998:25, 999:15</p> <p>sort^[20] - 672:20, 688:22, 707:2, 710:18, 711:10, 718:11, 740:1, 751:21, 757:5, 860:11, 898:2, 958:20, 971:3, 977:3, 977:4, 977:11, 985:17, 985:18, 988:24, 990:16</p> <p>sound^[1] - 827:4</p> <p>sounds^[3] - 694:2, 893:1, 895:8</p> <p>source^[1] - 749:1</p>	<p>space^[2] - 898:8, 898:9</p> <p>speaking^[2] - 726:1, 869:3</p> <p>special^[1] - 992:16</p> <p>specialize^[2] - 887:14, 887:15</p> <p>species^[2] - 840:14, 840:15</p> <p>specific^[4] - 694:11, 758:11, 786:8, 993:19</p> <p>specifically^[34] - 685:18, 703:8, 712:2, 717:24, 722:16, 722:17, 727:20, 728:1, 731:18, 756:21, 791:3, 794:13, 799:8, 799:9, 807:3, 814:17, 820:13, 855:13, 862:16, 865:13, 872:25, 875:24, 876:12, 876:19, 877:5, 881:16, 882:13, 884:5, 884:13, 888:14, 927:14, 939:15, 942:8, 942:10</p> <p>specification^[7] - 826:15, 827:8, 965:14, 966:4, 966:8, 967:10, 983:7</p> <p>specifications^[3] - 681:22, 967:14, 967:19</p> <p>specified^[1] - 762:25</p> <p>specifies^[2] - 808:16, 821:23</p> <p>specify^[1] - 808:15</p> <p>spectrometry^[1] - 989:25</p> <p>speculating^[1] - 857:11</p> <p>speculation^[1] - 792:22</p> <p>speed^[1] - 1001:5</p> <p>speeds^[1] - 987:1</p> <p>spells^[2] - 811:1, 896:16</p> <p>spend^[2] - 757:1, 866:3</p> <p>spending^[2] - 755:22, 811:11</p> <p>spent^[2] - 833:6, 838:2</p> <p>spike^[1] - 982:24</p> <p>spill^[19] - 842:17, 853:10, 853:13,</p>	<p>853:16, 883:7, 883:13, 883:16, 883:20, 899:20, 907:23, 910:18, 912:4, 913:12, 914:5, 914:11, 914:14, 924:8</p> <p>Spillover^[1] - 838:15</p> <p>spillover^[4] - 838:18, 840:17, 841:10, 842:8</p> <p>spills^[1] - 912:6</p> <p>splitting^[3] - 867:16, 867:20, 868:16</p> <p>sponsor/ collaborator^[1] - 739:7</p> <p>sponsors^[1] - 789:5</p> <p>spontaneously^[1] - 706:4</p> <p>sports^[1] - 866:2</p> <p>spots^[1] - 971:4</p> <p>spotted^[1] - 758:6</p> <p>Squibb^[1] - 674:10</p> <p>SSRIs^[1] - 862:12</p> <p>stabilization^[1] - 789:9</p> <p>stabilized^[1] - 901:15</p> <p>stack^[1] - 986:5</p> <p>stage^[1] - 965:1</p> <p>stand^[7] - 711:2, 741:14, 777:10, 777:21, 778:5, 895:16, 949:22</p> <p>standard^[6] - 692:2, 800:24, 805:1, 824:10, 834:11, 990:6</p> <p>standing^[3] - 760:10, 761:5, 888:6</p> <p>stands^[1] - 983:2</p> <p>staring^[1] - 845:3</p> <p>start^[24] - 705:4, 712:12, 712:14, 724:7, 758:14, 800:10, 824:10, 829:3, 830:10, 845:24, 847:8, 866:10, 867:14, 868:13, 895:10, 910:19, 924:11, 924:12, 938:8, 963:22, 984:17, 993:1, 999:18, 1001:22</p> <p>started^[5] - 702:13, 747:1, 757:24, 768:13, 949:8</p> <p>starters^[1] - 736:8</p> <p>starting^[4] - 810:4,</p>
--	---	--	---	--

<p>814:6, 819:19, 868:9 starts [2] - 867:11, 941:20 state [19] - 701:9, 705:24, 711:3, 809:12, 835:15, 860:8, 860:11, 889:2, 889:6, 889:10, 889:12, 889:13, 891:2, 891:11, 926:7, 927:8, 935:9, 998:9, 1000:1 statement [8] - 788:7, 831:2, 857:5, 860:24, 860:25, 878:21, 947:3, 947:6 Statement [2] - 758:8, 758:10 statements [2] - 873:2, 939:7 STATES [1] - 1:2 states [12] - 698:15, 785:24, 793:2, 795:11, 804:10, 806:7, 812:3, 812:18, 817:1, 817:9, 926:22, 942:17 States [2] - 747:12, 798:5 stating [1] - 882:22 station [1] - 898:8 statistically [5] - 870:17, 871:20, 871:24, 877:13, 884:19 status [1] - 693:16 statute [2] - 765:3, 766:3 stay [5] - 708:1, 868:17, 869:25, 908:17, 908:21 stayed [1] - 908:25 staying [1] - 844:19 stenographic [1] - 1003:25 Step [2] - 962:10, 962:21 step [29] - 680:24, 681:2, 693:19, 767:2, 770:16, 828:12, 893:12, 951:14, 951:15, 952:2, 952:3, 952:4, 954:1, 956:17, 956:18, 957:7, 957:8, 960:2, 960:3, 960:11, 960:12, 962:7, 962:19,</p>	<p>963:17, 963:18, 964:1, 964:3, 1002:16 steps [22] - 675:14, 681:2, 697:19, 766:14, 773:14, 796:15, 938:13, 942:12, 942:19, 942:23, 943:12, 943:15, 944:7, 947:15, 947:17, 952:11, 952:16, 956:9, 956:17, 957:7, 972:11, 1002:4 steps.. [1] - 952:14 stereoisomers [1] - 969:22 Steven [4] - 895:15, 896:2, 920:9, 938:1 STEVEN [1] - 895:21 sticking [1] - 939:23 still [18] - 674:2, 841:3, 858:5, 858:8, 858:15, 888:15, 900:2, 909:2, 913:21, 916:14, 916:15, 916:16, 920:4, 938:9, 943:19, 948:1, 953:18, 978:22 stimuli [5] - 889:3, 889:6, 889:11, 889:14, 889:20 stipulation [1] - 705:8 stipulations [1] - 800:4 STONE [68] - 671:9, 690:18, 697:7, 697:16, 697:22, 698:23, 699:1, 699:25, 758:7, 758:15, 758:18, 759:3, 759:10, 759:14, 760:5, 760:14, 775:21, 775:25, 776:7, 776:14, 894:22, 895:3, 895:14, 895:18, 895:24, 898:18, 898:23, 901:5, 901:9, 901:10, 902:13, 902:17, 902:19, 903:17, 903:18, 904:3, 904:7, 905:19, 905:22, 906:6, 906:7, 907:9, 907:11, 908:1, 908:3, 911:4, 911:8,</p>	<p>911:9, 919:6, 919:10, 924:16, 934:14, 935:25, 936:2, 937:22, 938:5, 938:11, 938:19, 940:2, 940:9, 940:14, 940:17, 943:2, 943:21, 944:1, 944:5, 944:10, 948:25 stone [7] - 697:5, 758:23, 769:8, 970:14, 895:13, 939:9, 939:15 stood [1] - 775:25 stop [6] - 844:1, 908:18, 943:4, 943:16, 951:21 stopped [1] - 769:12 straight [1] - 800:5 strategically [1] - 919:25 Strawn [1] - 741:19 streamline [1] - 800:4 stress [1] - 771:14 stretch [1] - 894:6 strike [3] - 958:15, 961:12, 993:1 striking [1] - 836:2 strong [3] - 722:17, 819:21, 820:5 strongly [5] - 710:22, 859:4, 859:5, 859:7, 859:8 struck [1] - 961:13 structural [3] - 971:24, 986:14, 986:18 structure [31] - 683:10, 969:16, 969:18, 969:22, 970:11, 970:14, 970:17, 970:22, 970:23, 970:25, 972:1, 977:5, 977:6, 977:8, 977:13, 977:15, 978:7, 979:23, 982:23, 983:3, 983:4, 983:21, 989:4, 990:7, 990:12, 990:19, 990:22, 995:8, 995:24 structures [8] - 682:3, 682:9, 861:10, 955:10, 955:24, 970:3, 979:20 studied [2] - 809:13, 924:6 Studies [1] - 961:17</p>	<p>studies [40] - 726:5, 728:19, 730:12, 746:14, 797:21, 799:3, 799:6, 827:9, 827:15, 833:2, 834:21, 863:1, 863:10, 891:17, 897:17, 897:24, 898:6, 898:20, 903:8, 909:13, 909:23, 910:2, 916:2, 916:4, 916:7, 918:4, 919:20, 922:21, 924:10, 929:2, 929:10, 933:3, 933:4, 968:13, 977:19, 987:22, 997:2, 997:4 study [55] - 714:18, 714:19, 719:14, 726:2, 728:24, 738:23, 739:7, 746:25, 756:10, 757:23, 757:24, 758:3, 774:17, 774:22, 778:16, 778:24, 779:18, 779:21, 780:19, 781:10, 784:5, 789:5, 789:16, 790:1, 790:5, 793:3, 793:5, 797:4, 797:21, 804:21, 826:14, 827:16, 827:23, 834:22, 848:5, 885:3, 891:17, 896:14, 903:12, 903:14, 904:11, 904:18, 906:15, 906:18, 906:25, 907:3, 919:21, 921:4, 924:13, 926:7, 926:23, 937:20, 938:6 studying [6] - 712:14, 719:16, 773:4, 804:10, 896:25, 902:22 stuff [3] - 688:6, 886:12, 945:18 subject [10] - 713:14, 714:18, 790:1, 855:16, 858:18, 934:22, 936:7, 958:3, 998:22, 1003:10 subjective [2] - 789:3, 997:23 subjects [17] - 809:12,</p>	<p>817:9, 852:1, 854:23, 855:17, 855:20, 856:3, 857:22, 904:23, 906:18, 906:19, 925:23, 926:9, 926:23, 927:2, 928:17, 928:22 Subjects [2] - 778:18, 789:20 submission [6] - 770:6, 775:17, 966:24, 967:5, 967:6, 981:13 submit [5] - 672:25, 740:5, 740:14, 748:25, 770:9 submitted [11] - 740:24, 747:4, 747:5, 779:24, 780:3, 787:11, 790:20, 791:8, 966:22, 981:9, 985:25 subsequent [2] - 909:13, 918:15 subsequently [2] - 957:23, 989:12 substance [12] - 695:9, 750:12, 750:25, 757:2, 771:23, 771:24, 795:21, 798:1, 922:25, 985:1, 985:12, 993:14 substances [2] - 985:1, 991:11 substantial [1] - 753:24 substantially [1] - 875:3 substantive [3] - 696:2, 860:22, 1003:17 subtle [1] - 971:22 succeed [1] - 811:15 succeeded [1] - 688:1 success [17] - 801:14, 810:24, 811:9, 814:10, 828:2, 878:17, 878:20, 879:1, 879:3, 879:6, 879:11, 879:13, 910:10, 953:15, 953:22, 978:8, 979:24 successful [5] - 718:3, 718:5, 804:15, 852:25, 903:9</p>
--	--	--	---	---

<p>successfully [3] - 715:23, 718:15, 932:14</p> <p>successive [1] - 756:11</p> <p>suddenly [1] - 699:8</p> <p>sufferers [1] - 862:20</p> <p>suffering [1] - 844:17</p> <p>sufficient [9] - 718:15, 718:18, 729:17, 748:11, 851:11, 919:21, 927:19, 983:6, 983:8</p> <p>suggest [13] - 729:4, 745:13, 745:23, 803:14, 803:23, 806:6, 809:19, 811:24, 813:11, 825:8, 825:24, 875:17, 876:2</p> <p>suggested [2] - 757:13, 954:25</p> <p>suggesting [1] - 846:15</p> <p>suggestion [2] - 687:18, 699:17</p> <p>suggests [4] - 755:24, 803:18, 804:9, 805:7</p> <p>suit [1] - 935:21</p> <p>suitable [1] - 812:8</p> <p>suites [2] - 799:23, 811:3</p> <p>sum [5] - 722:20, 785:7, 809:17, 824:3, 914:9</p> <p>summarize [8] - 701:20, 702:11, 715:18, 722:21, 800:12, 818:22, 820:14, 822:9</p> <p>summarized [3] - 803:9, 815:10, 953:7</p> <p>summarizes [5] - 799:5, 911:14, 921:4, 923:6, 923:12</p> <p>summarizing [9] - 703:21, 830:1, 899:11, 904:16, 919:18, 923:13, 950:19, 977:24, 979:10</p> <p>Summary [3] - 791:14, 791:16, 876:19</p> <p>summary [13] - 701:8, 727:9, 785:9, 789:12, 813:10, 863:22, 899:3, 901:12, 902:21, 904:18, 916:2, 923:22, 926:7</p>	<p>summary [1] - 906:13</p> <p>sun [1] - 898:9</p> <p>supervisor [1] - 904:1</p> <p>supplying [1] - 965:15</p> <p>support [3] - 687:25, 692:6, 748:11</p> <p>Support [1] - 961:16</p> <p>supported [1] - 796:2</p> <p>suppose [2] - 723:10, 834:3</p> <p>supposedly [1] - 763:23</p> <p>supposition [1] - 946:16</p> <p>suppress [1] - 868:4</p> <p>sur [1] - 695:18</p> <p>surface [1] - 691:5</p> <p>surprised [3] - 690:9, 730:22, 814:20</p> <p>surprisingly [1] - 828:19</p> <p>Surrey [1] - 896:13</p> <p>surrounding [1] - 861:2</p> <p>sustained [4] - 782:2, 782:3, 792:23, 961:11</p> <p>swear [2] - 764:16, 764:19</p> <p>switch [1] - 826:2</p> <p>sworn [1] - 700:22</p> <p>symbols [1] - 940:12</p> <p>symptomatic [1] - 900:1</p> <p>synchronization [2] - 709:17, 869:14</p> <p>Synchronization [1] - 900:22</p> <p>synchronize [2] - 714:21, 830:22</p> <p>synchronized [2] - 708:1, 869:17</p> <p>synonymous [3] - 806:9, 809:7, 821:8</p> <p>synthesis [3] - 956:8, 963:8, 993:9</p> <p>synthesize [2] - 683:15, 835:15</p> <p>synthesizing [3] - 956:15, 957:5, 959:20</p> <p>synthetic [6] - 724:8, 724:9, 831:6, 832:5, 832:10, 961:7</p> <p>system [3] - 695:20, 875:9, 926:11</p> <p>System [1] - 701:14</p> <p>systematic [1] - 917:3</p>	<p>T</p> <p>tab [12] - 755:8, 786:19, 786:20, 872:5, 880:23, 903:13, 906:3, 957:14, 965:8, 966:14, 973:15, 980:10</p> <p>table [11] - 855:13, 920:23, 920:25, 966:3, 986:4, 987:5, 987:8, 988:9, 988:15, 988:25, 989:7</p> <p>Table [3] - 805:3, 855:10, 863:19</p> <p>tabs [4] - 852:7, 859:15, 864:21, 906:2</p> <p>tackle [1] - 808:21</p> <p>takeaway [1] - 718:11</p> <p>talks [21] - 727:10, 727:25, 733:23, 733:24, 753:8, 799:19, 811:2, 816:10, 821:2, 821:4, 823:25, 826:16, 854:18, 857:9, 878:2, 878:6, 913:10, 929:2, 987:24, 991:1</p> <p>target [2] - 821:11, 848:16</p> <p>targeted [3] - 813:1, 816:24, 821:14</p> <p>tasi [1] - 935:12</p> <p>Tasimelton [3] - 778:17, 789:19, 845:19</p> <p>tasimelton [172] - 680:6, 680:20, 681:5, 681:21, 682:14, 684:14, 684:23, 685:1, 687:5, 687:17, 688:2, 688:25, 690:6, 703:17, 704:19, 705:1, 705:2, 705:4, 705:8, 709:22, 710:11, 710:19, 711:25, 724:6, 724:7, 724:23, 725:1, 725:25, 726:3, 727:14, 727:16, 728:20, 728:24, 729:10, 730:15, 730:17, 731:10, 736:12, 773:3,</p>	<p>773:5, 773:10, 774:21, 788:25, 789:1, 789:6, 796:9, 797:6, 797:7, 797:9, 799:1, 799:11, 799:12, 799:19, 799:22, 800:2, 803:21, 803:24, 806:13, 806:20, 807:2, 808:5, 808:13, 809:4, 810:9, 811:2, 811:7, 812:4, 812:18, 812:25, 813:5, 813:23, 814:13, 814:23, 816:7, 816:16, 816:23, 817:1, 817:17, 817:20, 818:11, 819:10, 819:20, 820:6, 821:5, 821:24, 823:2, 823:5, 823:8, 823:14, 823:15, 824:21, 825:9, 825:15, 825:16, 825:24, 826:17, 827:16, 827:19, 827:24, 829:21, 830:21, 832:24, 833:3, 833:11, 833:15, 833:24, 834:20, 837:16, 837:24, 845:10, 846:8, 846:16, 847:9, 847:24, 848:12, 849:8, 855:5, 856:4, 856:9, 858:21, 859:4, 861:16, 862:1, 864:9, 864:11, 865:20, 866:18, 870:8, 871:7, 872:20, 873:13, 875:2, 876:15, 877:9, 877:11, 879:17, 881:9, 882:23, 883:8, 883:19, 884:18, 925:10, 937:11, 951:4, 952:1, 956:8, 956:16, 957:6, 959:20, 960:8, 962:25, 965:6, 968:22, 976:16, 978:5, 978:16, 978:19, 979:1, 979:3, 984:25, 985:1, 985:12, 986:9, 991:11, 993:3, 993:10,</p>	<p>994:16, 997:20, 998:8, 999:21, 999:24, 1001:17</p> <p>tasimelton's [1] - 799:16</p> <p>task [1] - 702:22</p> <p>tau [4] - 847:3, 921:18, 921:25, 922:2</p> <p>teach [5] - 803:13, 803:23, 806:6, 811:24, 813:11</p> <p>teaches [4] - 679:25, 803:18, 804:8, 805:6</p> <p>teaching [2] - 701:17, 833:9</p> <p>teacup [1] - 678:19</p> <p>team [1] - 865:24</p> <p>teams [3] - 865:19, 865:23, 866:1</p> <p>technically [1] - 760:25</p> <p>Technology [1] - 961:16</p> <p>teed [1] - 770:20</p> <p>temperature [4] - 706:14, 708:7, 901:18, 901:20</p> <p>tempest [1] - 678:19</p> <p>ten [6] - 853:7, 906:15, 906:25, 908:9, 910:2, 944:23</p> <p>tendency [5] - 708:4, 708:7, 709:9, 709:12, 869:19</p> <p>tender [1] - 700:16</p> <p>tentative [2] - 969:16, 970:11</p> <p>tentatively [2] - 969:19, 989:6</p> <p>term [8] - 832:6, 842:7, 842:14, 891:5, 899:12, 907:15, 997:22</p> <p>termed [1] - 851:8</p> <p>terminology [3] - 705:25, 854:23, 854:25</p> <p>terms [11] - 706:1, 818:3, 824:13, 833:13, 844:21, 868:7, 889:18, 916:21, 923:6, 948:22, 963:9</p> <p>terrible [1] - 848:21</p> <p>test [2] - 683:14, 990:15</p> <p>tested [3] - 866:21, 870:5, 875:13</p> <p>testified [17] - 690:19, 700:22, 711:4,</p>
---	---	---	---	---

<p>777:22, 782:8, 782:16, 782:19, 794:9, 817:14, 825:6, 859:23, 881:20, 888:17, 895:22, 938:1, 956:7 testify [21] - 673:22, 673:25, 678:16, 699:24, 731:22, 732:16, 733:19, 736:24, 737:19, 739:25, 746:1, 748:8, 751:6, 757:2, 771:23, 771:24, 782:13, 782:18, 795:21, 881:15, 938:25 testifying [4] - 731:21, 732:22, 742:4, 882:20 testimonial [1] - 737:24 testimony [34] - 682:23, 688:5, 689:7, 692:4, 699:13, 699:18, 701:4, 701:8, 704:7, 711:16, 743:7, 743:12, 772:15, 789:25, 898:11, 901:25, 903:5, 940:11, 946:23, 948:20, 948:25, 949:1, 949:8, 949:20, 950:5, 950:10, 950:12, 951:7, 956:20, 958:15, 972:15, 976:12, 988:18, 988:23 testing [4] - 995:23, 996:3, 996:25, 997:17 tests [3] - 990:6, 996:15, 996:18 TEVA [1] - 1:7 Teva [11] - 671:6, 683:18, 980:8, 980:15, 981:12, 981:25, 982:2, 982:17, 982:22, 983:2, 992:6 Texas [1] - 735:13 text [10] - 786:15, 791:16, 830:10, 835:21, 856:12, 857:2, 870:24, 871:19, 873:4, 880:19 texts [1] - 875:1</p>	<p>THE [456] - 1:2, 1:3, 672:5, 672:13, 672:24, 673:5, 673:10, 673:21, 674:4, 674:21, 674:25, 675:6, 675:10, 675:15, 675:19, 676:7, 676:9, 676:17, 676:20, 676:22, 677:2, 677:6, 677:14, 677:18, 677:22, 678:8, 678:13, 678:23, 679:5, 680:16, 680:19, 680:22, 681:4, 681:7, 681:14, 681:20, 682:14, 682:16, 682:19, 682:22, 684:4, 684:14, 684:19, 685:6, 685:12, 685:16, 686:19, 687:1, 687:15, 689:3, 689:13, 689:18, 689:21, 689:23, 690:2, 690:11, 690:17, 691:7, 692:7, 692:19, 693:21, 694:1, 694:8, 694:12, 694:15, 694:23, 695:2, 695:4, 695:10, 695:17, 696:1, 696:6, 696:8, 696:10, 696:13, 696:17, 696:22, 697:3, 697:15, 697:21, 697:24, 698:5, 698:12, 698:20, 698:24, 699:19, 699:23, 700:3, 700:7, 700:9, 711:7, 711:12, 711:19, 713:11, 714:13, 715:13, 717:14, 718:18, 718:19, 718:20, 718:22, 719:11, 720:17, 721:21, 724:1, 725:18, 727:2, 730:8, 731:16, 732:5, 732:7, 732:18, 732:21, 733:5, 733:12, 733:17, 733:21, 734:2, 734:9, 734:14, 734:20, 735:3, 735:10, 735:20,</p>	<p>735:25, 736:3, 736:8, 736:11, 736:14, 736:20, 737:14, 738:16, 739:11, 739:19, 740:3, 740:8, 740:12, 741:2, 741:6, 741:9, 741:13, 741:22, 742:1, 742:9, 743:5, 743:21, 743:24, 744:4, 744:15, 744:20, 744:22, 744:25, 745:5, 745:13, 745:21, 746:8, 746:12, 747:9, 747:15, 747:20, 747:24, 748:3, 748:6, 749:4, 750:3, 750:20, 751:17, 752:3, 752:15, 752:20, 752:24, 753:3, 753:6, 753:17, 754:2, 754:8, 754:14, 754:23, 755:4, 755:10, 756:19, 756:23, 757:10, 758:5, 758:14, 758:17, 758:23, 759:4, 759:13, 760:4, 760:13, 761:9, 761:23, 762:5, 762:10, 762:15, 763:7, 763:10, 763:18, 763:21, 764:1, 764:4, 764:18, 765:9, 765:14, 765:20, 765:23, 766:10, 766:18, 766:21, 767:2, 768:2, 768:5, 768:12, 768:20, 769:6, 769:13, 769:16, 769:19, 769:22, 770:10, 770:13, 770:15, 772:9, 773:16, 773:21, 774:3, 774:6, 774:9, 774:12, 774:19, 774:24, 775:1, 775:12, 775:24, 776:6, 776:13, 776:17, 776:21, 776:24, 777:4, 777:8, 777:11, 777:13, 777:17, 777:20, 777:23, 777:25, 778:2,</p>	<p>781:16, 781:23, 782:2, 782:15, 783:3, 783:5, 784:20, 785:4, 786:1, 786:5, 787:25, 788:5, 788:15, 788:18, 788:21, 792:23, 793:11, 795:5, 795:8, 795:18, 795:24, 796:4, 796:11, 797:15, 798:21, 828:6, 828:10, 828:21, 830:7, 835:11, 844:25, 845:5, 850:7, 880:9, 880:13, 881:19, 881:24, 882:10, 886:9, 886:12, 886:14, 886:16, 886:19, 886:21, 886:22, 886:24, 886:25, 887:1, 887:4, 887:6, 887:10, 887:15, 887:20, 887:22, 887:25, 888:4, 888:9, 888:11, 888:15, 888:16, 888:17, 888:19, 888:20, 888:24, 888:25, 889:1, 889:7, 889:10, 889:15, 889:17, 889:21, 889:25, 890:22, 890:24, 890:25, 891:3, 891:4, 891:9, 891:21, 891:22, 892:8, 892:11, 892:12, 892:13, 892:14, 892:17, 892:20, 892:22, 892:24, 893:3, 893:9, 893:11, 893:12, 893:14, 893:15, 894:5, 894:19, 894:23, 895:1, 895:8, 895:13, 895:17, 895:20, 898:22, 901:7, 902:15, 911:6, 919:8, 924:18, 924:21, 934:16, 935:24, 937:23, 937:24, 938:4, 938:10, 938:18, 939:2, 939:8, 939:13, 940:1, 940:5,</p>	<p>940:13, 940:16, 940:21, 941:3, 941:6, 941:9, 941:14, 941:23, 941:25, 942:4, 942:7, 942:13, 942:16, 942:21, 943:4, 943:24, 944:4, 944:8, 944:18, 945:3, 945:5, 945:11, 945:15, 946:11, 946:17, 947:1, 947:10, 947:12, 947:19, 948:7, 948:13, 948:18, 948:21, 949:4, 949:11, 949:13, 949:19, 949:23, 949:25, 951:8, 951:10, 951:21, 951:25, 952:8, 952:20, 956:21, 956:23, 956:25, 958:5, 958:16, 959:3, 960:23, 961:1, 961:4, 961:9, 961:13, 964:15, 964:20, 964:22, 964:24, 965:21, 972:16, 972:17, 974:3, 975:14, 980:24, 981:17, 981:20, 984:4, 984:6, 984:9, 984:12, 998:5, 998:12, 998:16, 998:18, 998:25, 999:5, 999:9, 1001:22, 1002:13, 1002:22, 1003:2, 1003:6, 1003:15 themselves [1] - 892:7 then-ongoing [2] - 879:20, 880:4 theoretically [4] - 688:14, 921:11, 922:11, 922:17 theory [6] - 681:20, 687:1, 692:7, 692:9, 921:19, 921:20 therapeutic [2] - 718:1, 718:6 thereabouts [1] - 852:24 thereby [1] - 832:17 therefore [11] - 681:23, 713:22, 719:24, 795:4, 795:21, 799:23,</p>
--	--	--	--	---

<p>814:25, 818:5, 915:16, 985:11, 1002:5 thereof [1] - 766:5 they've [9] - 681:12, 685:12, 685:18, 707:24, 743:21, 761:24, 890:16, 892:5, 938:21 Thibodeau [4] - 934:19, 934:25, 935:5, 936:6 thinking [7] - 672:19, 675:2, 682:21, 765:24, 935:12, 937:11, 957:17 thinks [3] - 868:8, 868:9, 869:4 Third [2] - 749:3, 796:2 third [7] - 780:20, 806:12, 851:21, 893:17, 935:8, 975:18, 987:24 thirds [1] - 780:24 thoughts [1] - 907:6 three [18] - 704:22, 738:11, 761:1, 808:3, 809:25, 814:8, 864:21, 904:23, 904:25, 909:24, 919:20, 922:11, 927:4, 930:13, 946:6, 953:7, 969:21, 984:25 threshold [7] - 738:5, 994:11, 994:18, 994:19, 995:1, 997:10, 1001:3 thresholds [3] - 993:19, 994:2, 994:8 throughout [1] - 794:15 timed [4] - 905:6, 919:25, 930:8, 932:2 timeline [11] - 712:12, 712:21, 718:24, 720:4, 721:6, 722:20, 724:4, 724:12, 725:6, 729:20, 800:2 timelines [2] - 711:24, 712:6 timeliness [1] - 691:4 timing [18] - 707:9, 709:3, 709:5, 709:8, 723:8, 728:20, 728:22, 789:11, 807:24, 808:11,</p>	<p>810:12, 812:24, 816:22, 850:25, 867:17, 916:3, 916:7, 932:3 timings [1] - 923:15 tiny [1] - 688:3 tired [1] - 998:9 Title [2] - 791:4 title [12] - 725:23, 778:15, 789:18, 816:19, 817:8, 850:11, 852:14, 860:2, 918:23, 958:10, 961:19 titled [2] - 829:8, 850:16 today [17] - 701:4, 759:2, 759:20, 771:20, 776:10, 821:18, 834:22, 837:20, 837:23, 858:15, 895:1, 898:24, 899:4, 899:7, 923:13, 950:5, 1003:3 together [9] - 693:11, 756:9, 775:10, 842:10, 851:1, 851:7, 971:3, 986:6, 991:3 tomorrow [2] - 894:16, 1002:15 tone [1] - 891:19 tonight [1] - 1002:18 took [8] - 682:2, 693:4, 797:8, 831:23, 839:1, 895:18, 956:11, 1003:3 top [18] - 688:19, 722:9, 739:3, 746:6, 746:15, 747:18, 749:13, 778:4, 787:11, 790:19, 860:18, 874:17, 911:13, 966:23, 967:3, 968:24, 981:3, 986:5 topic [3] - 678:1, 708:13, 711:11 topics [1] - 703:7 total [8] - 785:7, 789:3, 789:7, 826:13, 855:14, 893:4, 967:13, 968:1 totally [23] - 707:22, 722:25, 731:11, 732:10, 738:4, 808:23, 809:7, 809:10, 811:7,</p>	<p>817:7, 817:9, 818:17, 818:19, 821:6, 830:16, 854:20, 890:2, 890:11, 904:19, 906:15, 926:23, 929:12, 932:14 Totally [2] - 778:18, 789:19 touch [1] - 694:14 touched [1] - 810:21 towards [1] - 786:21 toxic [4] - 683:24, 951:18, 953:14, 953:21 toxicity [1] - 977:19 trade [1] - 890:19 train [1] - 887:1 Transcript [1] - 1:15 transcript [2] - 752:17, 1003:25 transferred [1] - 693:13 transient [4] - 865:21, 866:19, 879:25, 885:6 transitive [1] - 795:19 translated [1] - 856:8 translation [1] - 921:12 travel [1] - 898:8 treat [25] - 703:17, 708:17, 708:21, 709:5, 710:4, 710:19, 720:23, 722:7, 722:10, 722:22, 724:5, 725:1, 728:1, 729:13, 729:15, 729:17, 731:11, 799:2, 845:10, 866:19, 885:17, 887:17, 892:15, 919:19, 925:6 treated [3] - 708:20, 847:8, 925:9 treating [26] - 701:19, 704:24, 705:2, 705:7, 719:25, 729:5, 799:17, 811:5, 812:8, 814:13, 815:3, 816:6, 819:9, 821:4, 821:23, 822:24, 824:22, 825:10, 825:14, 825:15, 827:20, 835:18, 843:25, 844:8, 882:23, 883:1 treatment [63] -</p>	<p>700:17, 702:22, 703:12, 704:11, 712:1, 713:22, 717:23, 719:25, 721:1, 721:3, 721:4, 722:2, 722:13, 722:18, 723:13, 726:9, 730:18, 789:6, 797:4, 799:23, 803:20, 805:12, 806:7, 806:9, 808:23, 810:7, 810:16, 811:3, 815:1, 817:21, 819:19, 819:20, 821:2, 825:25, 828:2, 832:3, 846:10, 846:16, 846:22, 847:10, 862:5, 899:21, 899:22, 906:20, 908:14, 908:18, 909:7, 914:22, 914:23, 915:22, 916:17, 924:11, 924:12, 926:9, 929:13, 931:10, 933:2, 962:10, 962:21, 964:3 Treatment [7] - 829:9, 838:15, 845:20, 900:24, 918:21, 931:20, 933:16 tree [1] - 977:3 tremendous [1] - 683:23 Trial [1] - 1:15 trial [66] - 672:3, 672:12, 685:7, 695:21, 696:23, 731:10, 736:9, 736:11, 738:6, 739:14, 739:16, 739:17, 740:5, 740:6, 740:7, 742:19, 746:21, 769:11, 770:11, 772:5, 772:11, 773:1, 773:2, 778:11, 779:9, 780:15, 783:20, 783:22, 785:9, 785:22, 788:23, 789:12, 789:23, 790:9, 790:17, 790:21, 792:19, 794:15, 797:1, 799:10, 799:13, 806:18, 806:19,</p>	<p>809:4, 811:7, 811:11, 811:16, 815:13, 816:20, 817:4, 817:6, 827:23, 833:5, 845:24, 846:8, 846:12, 878:6, 878:18, 878:25, 879:12, 879:20, 880:5, 885:24, 890:23, 905:3, 912:17 trial's [1] - 759:8 trials [24] - 761:16, 779:6, 798:4, 799:14, 800:22, 808:6, 813:4, 815:13, 816:8, 816:23, 816:25, 817:25, 818:8, 834:24, 878:3, 879:24, 880:16, 885:12, 885:23, 897:21, 900:1, 904:4, 917:4, 936:17 tried [7] - 680:11, 683:8, 728:25, 738:8, 748:15, 853:2, 916:5 triggered [1] - 867:24 trivial [1] - 966:11 trouble [4] - 878:24, 986:22, 995:16, 995:23 true [11] - 686:21, 755:21, 757:12, 761:6, 762:23, 776:5, 776:10, 841:10, 903:1, 922:20, 1003:24 truth [3] - 731:19, 732:22, 761:1 try [13] - 748:16, 769:25, 772:24, 775:20, 848:21, 849:13, 876:3, 892:19, 894:20, 899:7, 913:12, 921:9, 996:8 trying [27] - 674:22, 680:1, 687:23, 697:9, 697:13, 708:23, 708:25, 738:16, 748:4, 756:3, 766:21, 790:3, 831:18, 838:3, 884:24, 905:20, 912:7, 915:17, 915:19, 917:1, 949:5, 949:6,</p>
--	---	--	--	--

<p>961:6, 964:18, 988:22, 1001:5 TUNNELL [1] - 671:12 turn [55] - 712:22, 713:25, 714:24, 716:6, 716:14, 716:20, 717:1, 718:25, 720:4, 721:7, 723:14, 724:13, 725:6, 726:13, 728:7, 729:21, 731:1, 754:16, 779:10, 793:23, 797:14, 849:17, 854:8, 859:13, 863:3, 876:20, 877:17, 900:15, 910:20, 917:12, 920:6, 936:4, 942:14, 956:6, 957:13, 959:11, 961:25, 963:11, 964:5, 965:7, 965:8, 966:14, 967:1, 967:7, 969:3, 972:19, 973:15, 974:15, 975:1, 975:17, 976:19, 978:12, 980:10, 983:11, 984:20 turned [1] - 944:1 turning [1] - 955:14 turns [4] - 686:1, 691:20, 746:15, 772:15 tutelage [1] - 886:22 two [82] - 672:8, 680:24, 681:2, 684:2, 688:5, 690:25, 708:22, 713:20, 713:22, 742:14, 753:25, 754:3, 754:6, 772:21, 780:24, 785:20, 806:25, 808:12, 809:5, 809:6, 811:21, 819:11, 819:13, 819:24, 822:4, 822:14, 823:19, 824:3, 826:12, 829:12, 834:24, 839:6, 839:25, 851:7, 852:7, 857:14, 857:16, 857:25, 858:6, 858:23, 859:15, 860:18, 861:18, 864:20, 866:11,</p>	<p>870:23, 880:23, 886:9, 887:18, 890:17, 891:12, 892:1, 894:24, 895:5, 897:11, 903:8, 906:2, 906:19, 908:23, 916:8, 919:22, 920:1, 939:6, 940:10, 950:19, 952:15, 956:9, 956:16, 957:6, 964:8, 966:7, 970:18, 970:20, 971:3, 971:4, 971:22, 974:16, 987:12, 989:15, 994:12, 998:19 two-minute [1] - 895:5 two-step [1] - 680:24 two-thirds [1] - 780:24 type [2] - 783:8, 918:8 types [2] - 810:10, 814:15 typically [7] - 734:6, 734:7, 867:15, 869:7, 971:20, 990:11, 991:14</p>	<p>949:24, 955:12, 956:1, 959:17, 961:20, 962:15, 974:7, 996:8 undergraduate [3] - 701:22, 886:17, 955:2 underlies [1] - 684:24 underlying [2] - 720:1, 931:15 underneath [2] - 792:10, 792:14 understood [14] - 672:18, 737:8, 737:16, 738:15, 751:20, 755:18, 756:4, 761:25, 802:21, 858:6, 916:12, 917:24, 946:12, 949:16 undisclosed [9] - 678:4, 733:15, 742:8, 951:7, 956:19, 958:14, 960:22, 964:13, 972:15 undone [1] - 914:5 unequivocally [3] - 691:12, 695:2, 695:3 unfortunate [1] - 771:16 unhelpful [1] - 843:5 unified [1] - 1001:24 unique [2] - 843:25, 844:6 United [2] - 747:12, 798:5 UNITED [1] - 1:2 universities [1] - 888:2 University [4] - 701:16, 701:23, 701:25, 896:13 unknown [2] - 950:16, 983:7 unless [8] - 679:8, 688:17, 732:10, 732:23, 733:2, 742:11, 748:8, 767:10 unlike [1] - 948:15 unnamed [1] - 892:2 unquote [1] - 761:19 unresponsive [1] - 893:6 untimely [5] - 759:18, 781:25, 785:1, 785:20, 788:3 unusual [2] - 761:4, 796:11</p>	<p>up [121] - 672:20, 675:17, 685:24, 688:25, 695:21, 700:9, 700:13, 706:24, 708:24, 709:1, 722:9, 722:20, 733:4, 735:14, 741:17, 744:14, 744:23, 745:11, 745:21, 745:22, 746:6, 750:21, 752:4, 752:24, 757:6, 759:23, 760:17, 761:5, 765:23, 769:10, 770:20, 777:6, 783:2, 783:6, 787:7, 801:23, 802:10, 809:17, 824:3, 826:3, 826:22, 827:13, 829:4, 830:9, 836:23, 841:16, 846:4, 850:11, 852:13, 854:5, 860:1, 864:25, 868:15, 868:17, 868:20, 870:22, 871:5, 872:15, 872:19, 876:3, 876:21, 876:24, 880:10, 882:12, 883:25, 884:12, 888:24, 893:15, 900:11, 904:4, 910:5, 912:15, 914:9, 923:9, 924:19, 925:14, 934:11, 936:19, 939:2, 941:2, 941:15, 950:7, 955:22, 957:23, 958:9, 958:10, 959:16, 959:21, 959:22, 961:19, 962:1, 963:3, 963:12, 964:5, 966:18, 966:23, 967:3, 967:12, 967:22, 968:1, 968:24, 969:4, 972:4, 972:23, 974:6, 974:16, 975:18, 976:1, 976:11, 981:10, 981:23, 986:4, 986:5, 990:20, 994:3, 996:14, 999:11, 1001:6, 1002:23 update [5] - 740:20,</p>	<p>745:14, 768:10, 780:25, 791:10 updated [6] - 740:14, 763:14, 767:7, 768:3, 770:4, 786:16 updates [3] - 740:14, 763:16, 778:10 upper [6] - 738:25, 763:21, 846:1, 861:13, 861:16, 994:12 upset [1] - 697:6 upstream [1] - 942:25 uptake [1] - 862:11 URLs [1] - 762:25 US [8] - 740:11, 745:3, 749:1, 752:2, 795:10, 795:16, 826:25, 885:4 US20170190683A1 [1] - 982:8 USA [1] - 1:7 usage [1] - 805:25 useful [9] - 675:4, 713:22, 726:9, 730:18, 730:23, 813:25, 814:13, 814:16, 814:25 uses [2] - 772:22, 1001:12</p>
				<p>V</p>
				<p>VA [2] - 701:14, 701:18 Vachharajani [2] - 725:11, 725:21 vaguely [1] - 775:17 validity [9] - 703:16, 703:18, 704:2, 705:9, 800:13, 819:3, 820:15, 822:17, 825:17 value [3] - 683:11, 683:23, 877:13 Vanda [71] - 671:13, 673:13, 675:17, 676:15, 677:9, 677:12, 681:23, 682:1, 682:13, 683:6, 683:21, 683:25, 684:9, 684:12, 684:25, 685:3, 685:20, 686:2, 687:5, 687:11, 687:13, 688:4, 688:5, 692:12, 692:20, 692:24, 693:4, 693:13, 693:15,</p>

703:4, 726:18,
727:6, 736:9, 739:7,
757:25, 761:11,
765:24, 766:14,
770:2, 770:3, 770:8,
771:14, 775:15,
796:17, 800:21,
825:8, 827:9,
878:10, 895:14,
947:16, 947:24,
950:23, 965:14,
966:5, 968:7, 969:5,
970:14, 970:20,
972:1, 973:12,
973:20, 974:18,
975:6, 975:20,
975:25, 976:3,
985:5, 985:25,
988:23, 989:2, 989:8
VANDA [1] - 1:5
Vanda's [13] - 692:24,
765:4, 770:6, 772:7,
802:12, 814:4,
848:4, 937:25,
965:7, 966:13,
968:22, 969:1,
974:24
variability [5] -
908:10, 910:10,
916:3, 923:17,
924:10
variation [1] - 899:21
varies [1] - 915:23
variety [1] - 706:5
various [10] - 767:22,
860:14, 864:4,
864:5, 865:10,
873:19, 916:9,
985:6, 986:8, 987:8
vary [2] - 837:10,
857:6
vast [1] - 735:6
vehicle [1] - 678:25
verbal [1] - 991:19
verity [1] - 734:13
version [32] - 740:15,
740:23, 741:11,
744:14, 745:25,
747:2, 747:6,
747:23, 756:14,
762:12, 765:11,
765:12, 765:14,
765:19, 765:21,
768:23, 769:2,
770:13, 770:14,
777:2, 782:9,
782:16, 787:10,
787:19, 790:17,
790:21, 795:11,
796:25, 874:12,

890:20, 935:2, 935:3
versions [5] - 740:16,
767:22, 788:14,
798:4, 934:25
versus [8] - 751:24,
825:15, 827:17,
837:13, 844:21,
884:20, 899:9, 971:2
vertical [2] - 908:17,
909:2
View [1] - 786:12
view [19] - 675:21,
676:11, 682:10,
683:8, 683:17,
687:8, 691:17,
691:25, 732:25,
735:17, 786:13,
786:15, 802:19,
819:12, 878:23,
881:21, 894:3,
953:3, 979:16
viewpoints [1] -
705:10
Views [3] - 784:11,
784:16, 786:6
views [1] - 786:15
visited [4] - 782:23,
784:3, 787:2, 787:9
volunteers [1] -
879:24

W

wait [13] - 672:15,
673:21, 690:11,
698:13, 744:15,
747:20, 752:24,
754:2, 758:22,
772:4, 946:11
waive [1] - 776:14
wake [12] - 707:13,
708:6, 708:24,
709:1, 802:10,
804:13, 804:16,
805:9, 805:19,
868:15, 868:20,
885:7
Wake [9] - 778:19,
783:16, 789:20,
816:11, 818:9,
829:9, 900:23,
918:22, 931:11
wakefulness [6] -
706:15, 706:20,
706:21, 707:17,
708:25, 728:23
walk [5] - 899:15,
908:7, 923:25,
941:15, 941:16
wall [3] - 898:2,

914:23, 915:5
wants [5] - 739:21,
767:11, 777:16,
942:9, 942:10
warranted [1] - 693:16
wasted [1] - 750:11
Watson [1] - 980:16
waves [3] - 890:7,
891:19, 892:5
Wayback [31] -
734:21, 735:1,
735:3, 735:4,
742:24, 742:25,
743:4, 743:12,
743:17, 743:22,
743:25, 744:10,
744:11, 757:12,
758:11, 760:7,
760:8, 762:1, 762:2,
762:8, 763:25,
766:8, 766:20,
766:22, 767:11,
768:6, 768:8,
769:17, 769:19,
776:4, 776:11
ways [2] - 891:12,
990:12
wear [1] - 887:18
web [5] - 731:7, 731:8,
745:22, 762:12,
783:7
website [77] - 733:7,
735:6, 740:8,
740:10, 740:11,
741:5, 742:6,
744:22, 744:25,
745:1, 745:2, 745:4,
745:11, 747:4,
747:5, 747:7,
747:10, 747:17,
748:1, 748:14,
748:21, 749:1,
749:6, 749:19,
750:10, 752:2,
752:7, 752:10,
752:19, 752:23,
753:20, 754:10,
754:20, 755:3,
755:7, 755:12,
755:19, 756:1,
757:6, 757:8,
757:19, 760:9,
760:12, 761:4,
763:3, 763:11,
763:13, 767:6,
767:7, 767:9,
767:15, 768:1,
768:24, 770:7,
771:25, 772:15,
772:16, 775:5,

778:12, 781:22,
785:10, 785:12,
785:15, 785:17,
788:10, 788:13,
789:13, 789:15,
790:4, 792:20,
795:10, 795:17,
795:25, 797:19,
797:20, 797:22,
798:2
website's [1] - 798:5
websites [1] - 744:2
Wednesday [1] - 1:14
week [3] - 706:1,
741:23, 950:9
weeks [8] - 764:8,
789:4, 846:10,
846:13, 847:9,
906:19, 908:22,
927:4
Weir [47] - 840:19,
844:24, 846:3,
847:20, 850:10,
851:19, 852:13,
853:8, 855:9, 860:1,
860:18, 861:8,
864:24, 866:12,
870:22, 872:16,
876:24, 902:17,
903:17, 906:6,
907:10, 958:9,
959:16, 959:21,
961:19, 961:25,
963:1, 963:11,
964:5, 966:17,
966:23, 967:3,
967:22, 968:17,
968:25, 969:3,
969:13, 970:6,
974:6, 974:16,
975:17, 975:25,
976:10, 981:2,
981:10, 981:16,
981:23
WEISS [1] - 671:8
welcome [3] - 865:20,
950:2, 994:4
well-known [2] -
829:16, 865:6
well-respected [1] -
928:4
wells [2] - 946:23,
956:11
WELLS [1] - 671:4
WHARTON [1] - 671:8
wheelhouse [1] -
858:13
whereas [2] - 970:13,
995:16
whereby [1] - 837:16

wherewithal [1] -
775:13
whichever [1] - 995:3
White [3] - 762:21,
765:17, 767:4
white [4] - 829:4,
871:21, 941:6,
999:20
whoa [3] - 943:4
whole [6] - 680:4,
686:4, 745:20,
750:16, 770:21,
793:20
wide [1] - 706:5
WILLIAM [1] - 671:5
willing [5] - 755:4,
755:12, 767:10,
771:13, 878:24
Wilmington [1] - 1:14
window [3] - 718:1,
718:6, 854:2
winning [1] - 944:11
Winston [1] - 741:19
wish [1] - 853:21
wishes [1] - 841:7
withdraw [2] - 831:4,
851:16
withdrawn [2] - 917:7,
918:16
withhold [2] - 948:8,
956:21
witness [40] - 679:14,
679:16, 690:18,
694:17, 694:20,
697:12, 699:6,
699:25, 700:1,
700:12, 700:21,
736:15, 736:17,
736:19, 737:18,
743:8, 749:7,
750:12, 751:6,
768:14, 771:23,
775:6, 777:10,
778:5, 782:13,
790:11, 797:23,
828:5, 828:12,
893:20, 894:15,
905:21, 924:17,
937:25, 938:12,
941:17, 946:18,
1003:13, 1003:16
WITNESS [38] -
718:19, 718:22,
777:25, 835:11,
845:5, 886:12,
886:16, 886:21,
886:24, 887:1,
887:6, 887:15,
887:22, 888:4,
888:11, 888:16,

888:19, 888:24, 889:1, 889:10, 889:17, 889:25, 890:24, 891:3, 891:9, 891:22, 892:11, 892:13, 892:17, 892:22, 893:3, 893:11, 893:14, 937:24, 949:25, 956:23, 964:24, 972:17 witnesses [3] - 755:20, 845:1, 894:25 WO [1] - 814:6 Women's [3] - 702:15, 896:3, 897:20 word [4] - 760:25, 829:24, 878:5, 940:15 Word [2] - 934:25, 935:2 words [22] - 676:22, 678:9, 684:11, 685:2, 698:13, 742:17, 749:7, 761:1, 765:2, 773:9, 781:15, 785:5, 789:5, 804:12, 818:1, 824:15, 842:5, 847:1, 853:23, 883:16, 889:21, 918:22 workings [1] - 784:25 works [12] - 677:9, 695:20, 740:1, 744:1, 755:8, 781:22, 785:14, 788:11, 828:10, 834:15, 875:18, 986:24 world's [1] - 841:24 worry [1] - 844:19 worth [1] - 755:22 wrap [1] - 876:3 write [1] - 936:24 writes [1] - 944:24 writing [2] - 759:24, 832:22 written [6] - 703:6, 721:13, 824:8, 824:12, 825:20, 838:19 wrote [4] - 775:22, 829:3, 829:25, 842:10 www [1] - 783:8	X XYZ [1] - 740:20 Y year [19] - 684:23, 714:6, 714:16, 715:16, 716:12, 717:7, 719:14, 720:10, 721:14, 730:2, 744:7, 744:8, 764:6, 764:12, 776:2, 903:8, 925:17 years [18] - 682:2, 683:7, 702:12, 702:14, 761:8, 769:8, 785:20, 838:2, 838:5, 838:9, 839:1, 840:6, 858:19, 887:24, 932:13, 948:4, 966:7, 985:21 yellow [5] - 816:11, 819:8, 821:3, 822:23, 871:22 yesterday [10] - 672:19, 674:8, 675:2, 678:21, 683:3, 689:7, 691:1, 697:20, 699:13, 950:12 yoked [1] - 851:1 York [1] - 885:15 young [3] - 697:11, 938:7, 981:17 YOUNG [57] - 671:9, 940:25, 941:8, 941:19, 941:24, 942:3, 942:6, 942:10, 942:14, 942:17, 942:24, 943:20, 945:1, 945:4, 946:7, 946:12, 946:20, 947:5, 947:11, 947:16, 948:2, 948:19, 948:22, 949:6, 949:12, 949:14, 950:1, 951:12, 952:6, 952:25, 957:3, 958:8, 959:1, 959:5, 959:6, 961:2, 961:6, 961:14, 964:17, 964:21, 965:3, 965:23, 968:16, 968:19, 972:18, 973:25, 974:5, 975:11, 975:16,	980:21, 981:1, 981:19, 981:21, 983:25, 984:3, 984:5, 984:7 yourself [6] - 675:18, 701:1, 771:12, 809:22, 835:4, 896:1 Z zero [1] - 893:16 zone [2] - 853:17, 912:6 zoom [3] - 882:16, 884:13, 936:18
---	--	---